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"Dyspituitarism": Twenty Years Later

WITH SPECIAL CONSIDERATION OF THE PITUITARY ADENOMAS

HARVEY CUSHING, M.D.
BOSTON

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"DYSPIUITARISM": TWENTY YEARS LATER
WITH SPECIAL CONSIDERATION OF THE PITUITARY ADENOMAS

HARVEY CUSHING, M.D.

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While so much that is new and important is being accomplished by younger men, it is a great compliment to be asked a second time to deliver one of these lectures; and in venturing to address you again on the same topic as before, I can only plead that in spite of unavoidable and often protracted interruptions, it has continued to engage much of my time and thought. Were every lecturer made to understand that after the lapse of twenty years he would be requested by the Society to give an accounting of his original thesis to see what, if anything, it had amounted to in the interim, such a program would, to say the least, foster conservatism of statement at his inaugural appearance.

At a meeting of the Society on December 10, 1910, under the title "Dyspituitarism," the attempt was made to throw some light on an obscure subject—the disorders of pituitary function—then of interest to few. Of that address, which I have forced myself to reread, the less said the better. It was soon amplified into a book, long since washed away in the ever increasing flood of hypophysial literature, now pouring over the dam, and to which all departments of medicine in clinic and laboratory are adding their quota.

I scarcely recall what first led us, soon after the opening of the Hunterian Laboratory in Baltimore in 1905, to attack such an unpromising problem.* It had its surgical aspects, to be sure, in that all pituitary

The Harvey Society Lecture, as given in part, Jan. 19, 1933, at the New York Academy of Medicine.

* Alfred Fröhlich and I had been co-workers in Sherrington's laboratory in Liverpool in 1900, in which year, unknown to us, Babinski¹⁰ had reported, under the title, "Tumor of the Pituitary Body Without Acromegaly," the case of a girl of 17, showing, at autopsy, arrested development of the organs of generation. In the following year, Fröhlich reported,⁵⁶ under an almost identical title, an example of the same syndrome in a boy of 16, the nature of the lesion not having been verified. In December, 1902, there died in Dr. Osler's wards at the Johns Hopkins Hospital a sexually undeveloped girl of 16 with the symptoms described by Babinski, and whose case was subsequently reported in my first paper which in any way pertained to the pituitary body.³³ While Babinski unquestionably is entitled to full priority in regard to this syndrome, it was popularized in Vienna through the interest aroused by the discussion of Fröhlich's paper.

disorders then known were somehow associated with tumors, but they were supposedly uncommon and because of their situation hopelessly unapproachable.

Just what might be the syndrome—if there was such a thing—of lost or impaired pituitary function was unknown. Indeed, there was no certain proof that Marie's acromegaly was not an expression of glandular deficiency. To be sure, certain states, called "adipositas cerebialis" (Schuster) and "adiposogenital dystrophy" (Bartels) had been the subject of discussion. But it seemed highly questionable whether these peculiar adiposal syndromes, which were sometimes associated with diabetes insipidus, had anything to do with the pituitary body; and whether they had any relation to acromegaly, in which malady gross hypophysial tumefactions might or might not be found after death, was still more doubtful.

Many were inclined to ascribe pituitary disorders to some perversion of secretion rather than to a quantitative loss or increase of the normal secretory product, whatever that might be—if indeed there actually was any such product in the anterior lobe. Though the belief had already been expressed by Benda¹⁶ (1900) that hyperplasia of acidophilic elements, apparently in a stage of secretory activity and therefore representing an adenoma, was a distinctive feature of acromegaly, others (e. g., Dean Lewis⁸¹) described an acidophilia apparently without adenomatous delimitation. However, at the time of which I speak, pathologists took little interest in the adenopathies as such, and most of the soft cellular unaccountable enlargements of the gland were regarded as sarcomas, or the noncommittal term "struma pituitaria" was applied to them.

With our knowledge of the pituitary disorders in this chaotic state, it was learned in the course of a series of operations on the canine hypophysis that enucleation of the posterior lobe (surprisingly enough, in view of its proved pharmacodynamic properties) caused no appreciable effect, whereas in adult animals a peculiar form of fatal cachexia supervened when the entire gland was removed. The fatal issue we thought could be postponed by glandular implantations or by injection of emulsions;⁸¹ but what was of greater significance, it was finally observed that those animals which had recovered after subtotal extirpations of the gland tended to become obese and sexually dystrophic—an experimental state comparable to adiposogenital dystrophy.⁸⁴

And when shortly after this it was reported, first by Bernhard Aschner⁷ (1910), that immature puppies not only tolerated hypophysectomy better than adult animals but remained dwarfed and sexually infantile, it was obvious that the syndrome of Fröhlich was truly a

deprivation disorder, suitably called *hypopituitarism*. This having been established, it was highly probable, all things considered, that acromegaly must represent the counter state of *hyperpituitarism*; indeed, one or two partly successful operations for acromegaly had led to an apparent amelioration of symptoms shown by a shrinkage of the hypertrophic hands and feet.

At the same time, it was clinically apparent that all examples of pituitary disease did not unmistakably fall in these two categories; certain adipose and sexually dystrophic adult patients with undifferentiated pituitary "strumas" might show traces of antecedent, or what has since been described as "fugitive" acromegaly,¹¹ while others in whom acromegalic changes had become pronounced tended in time to become fat and amenorrheic or impotent. These mixed syndromes consequently were taken to represent intermediary or overlapping states of disordered function conveniently classified as examples of *dyspituitarism*—whence the title of my former lecture.

While this conception of the pituitary disorders appeared at the time to be a satisfactory working basis, its weak points soon became apparent. Erdheim⁴⁸ had already (1904) shown that the usual tumor causing the syndrome of Fröhlich was of congenital origin, and suprasellar in situation; and since it was prone to deform the interbrain, he was led to attribute the syndrome largely to a diencephalic rather than a glandular source. On this basis, the acute cachexia as well as the more chronic adiposity and sexual dystrophy my co-workers and I had described³² might conceivably have been due to unavoidable hypothalamic contusions produced by Paulesco's intracranial method of approaching the gland, which we had adopted.

While it was not then known that the functional interdependence of hypophysis and hypothalamus is such that they can scarcely be discussed separately,³⁷ nevertheless, from these early canine experiments there were glimmerings, solely from a hypopituitary or deprivation aspect, to be sure, of an important influence exercised by the anterior lobe on the factors of growth and of sex. At the same time, striking secondary changes, particularly in the thyroid gland, had been observed, together with a greatly increased tolerance for carbohydrates, which needed explanation.^{60, 134}

It is incredible that from so small and unpromising an acorn there should have sprouted—or appear to have sprouted—in so short a time as twenty years such a far reaching and diversified plantation of interests. The literature of the subject in its many ramifications has become so enormous no one can pretend to keep pace with it, far less to comprehend it all in view of the contradictions and subtleties—not to say speculations—with which it has become enmeshed.

Attention has periodically switched from a consideration of the gland as a whole, to the posterior lobe, to the anterior lobe, and back again to a study of the separate properties of extracts of anterior or posterior lobe or of the tuberal cuff, and to the effect on them of hypothalamic stimulation or paralysis.

Some few have worked upstream to explore the central neuroglandular mechanisms that are involved, but a far greater number have worked downstream to examine the isolated effects of extracts on remote tissues and subsidiary organs. A fly could scarcely be cast anywhere in these waters, even by a novice at research, without hooking something deserving of experimental study; and for this purpose a goodly percentage of the animals in the ark, the amphibians below it and the doves about it have successively been utilized.

Out of all the present welter of discovery relating to the internal secretions, it becomes increasingly evident that the pituitary gland holds a dominating position in the endocrine series and exercises direct or indirect control over an unsuspected number of biochemical processes of utmost importance to the economy of the body. And should one venture to single out, from many, those particular steps that in recent years did most to accelerate our progress, they were the discovery in the anterior lobe of the two separable hormones of growth and sex. For these steps the brilliant experimental studies of Herbert M. Evans, on the one hand, and of Philip E. Smith, on the other, each with his several collaborators, were largely responsible.

But it is one thing to make discoveries through animal experimentation and quite another to correlate them with disease, and there is great need of an integrator to lead by the hand, through the present maze of scientific investigation, those who must deal with the victims of disordered pituitary function at the bedside. Were all human beings, male and female, as much alike as are standard rats of either sex, the clinician's difficulties might be ameliorated. Yet even rats of the purest strain show marked individual variation and fail to react precisely alike when injected with a pituitary hormone, whereas Nature's experiment of a similar kind on isolated examples of our own highly mongrel species may give results so bizarre they as yet exceed all power of interpretation.

To some of the etiologically obscure maladies that already have come to be laid at the door of pituitary dysfunction I shall have occasion to allude, and we may confidently expect that many more hitherto unexplained pathologic states will prove in time to be related to the neuro-biochemical imbalance of this amazing gland. But the field is now so large it would be futile in a single address to cover more than a small corner of it; and, surmising that a consideration of the adenomas and

their effects would at this time be as likely as any other to be of general interest, I shall confine myself to this single topic.

Pituitary Adenomas.—For an understanding of these tumors we must necessarily begin with the cellular composition of that portion of the gland which Berblinger chooses to call the adeno-hypophysis* to distinguish it from the neurohypophysis. While much unquestionably remains to be learned of the life history of the adeno-hypophysial cells (by perfected stains or by methods of intravital study or artificial cultivation as yet undeveloped), in the normal adult gland only three cellular elements, as originally described by Schönemann (1892), continue to be distinguished by histologists. More properly speaking, however, they represent a single or chief element in two differing stages of activity.

This chief element, the primary mother-cell, possesses a finely granular, nonstaining (chromophobe) cytoplasm, which in the process of ripening acquires coarse secretory granules of two distinguishable types known as acidophilic and basophilic† from their peculiar reactions to dyes. What is more, these ripened cells, as Severinghaus has recently shown,¹¹² not only have their individually characteristic paranuclear Golgi apparatus (that of the basophilic elements being distinguished by a ring; that of the acidophils by a filamentous net), but the predetermination of the change into basophilic or acidophilic elements is actually indicated (cf. fig. 1) by the morphology of the Golgi body in the mother-cell—an important disclosure to which I shall return (cf. p. 496).

* This convenient term, occasionally used herein, permits one to escape from the awkward employment of "anterior-pituitary" as an adjective which even abbreviated to A. P. has come into common use. To the uninitiated, much of the recent German literature has become unreadable from the employment of such codes. In his recent comprehensive monograph,²¹ Berblinger particularly emphasizes the functional unity of the adeno-hypophysis, the anatomic subdivisions of which (*pars anterior, intermedia et tuberalis*) he believes to be indistinguishable in man. But while this may be anatomically correct, it is physiologically embarrassing since there is every reason to believe that the neurohypophysis is activated by the enveloping portion of the adeno-hypophysis, and they can scarcely, therefore, be separately discussed.

† A fourth and a fifth element (the "pregnancy cells" of Erdheim and Stumme and the "castration cells" of Zacherl) are recognized, and numbers of highly similar cells are present in the gland in states of thyroid insufficiency. They all appear to be merely enlarged mother-cells which are arrested in the process of ripening through the exigencies of the physiologic state that produces them. Whether they are forerunners of acidophilic or of basophilic elements is disputed, and this may vary in different species. The nature of the Golgi bodies in the different types would probably decide the question.

The chromophobe mother-cells normally outnumber the others* and, as the character of their cytoplasm would indicate, appear to give off no secretory product, whereas the acidophilic and the basophilic elements unquestionably are in the process of elaborating, each its own peculiar active principle. We furthermore have fairly conclusive evidence that the separable growth-promoting principle is derived from the acidophilic elements, and there is some indirect evidence which suggests that the sex-maturing principle may be associated with the basophilic elements.

So far, this would seem simple enough: three distinguishable cell types—two of them actively secreting—a hormone accredited to each.

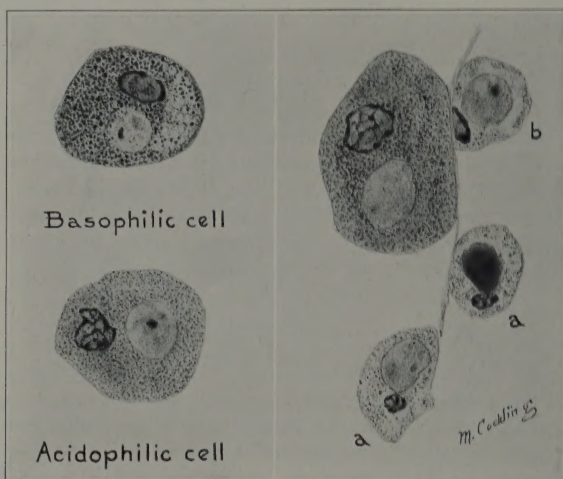


Fig. 1.—Drawing from hypophysis of monkey to show: (left) acidophilic "net" and basophilic "ring" types of Golgi, and (right) large acidophilic cell with three chromophobe elements (*b*) basophilic, (*a*) acidophilic.

But we unhappily are not permitted rest at this point, for highly competent observers are convinced that the anterior pituitary gives off several other separately identifiable hormones. This must mean either that there are more types of secreting cells in the gland than heretofore believed, or else that the ripened product of the two known types has a variable action under different circumstances. It is conceivable that

* Rasmussen¹⁰⁴ finds in the "normal" gland 52 per cent chromophobe, 37 per cent acidophilic and only 11 per cent basophilic cells.

the secretory product of a given cell may not always have precisely the same chemical formula, or even that a cell may discharge a cytoplasm of variable quality in different stages of ripening. But neither of these possibilities seems at all probable, and some other explanation may be forthcoming.

Now what, from a clinicopathologic standpoint, is highly significant in connection with this is the fact that only three types of pituitary adenomas are recognized: One is composed of chromophobe elements apparently identical with the nonsecreting mother-cells; in another, acidophilic elements abound, its clinical manifestations being those of overgrowth, while the third is purely basophilic in composition, its astonishing effects being conceivably ascribable to an excess of the gonad-stimulating principle. It is possible, of course, that those who have chiefly studied these pituitary adenomas have been influenced by preconceived ideas of what they should find, and there may be more types than have as yet been identified, but this appears unlikely. We, therefore, have neither cell type nor corresponding adenoma formations to represent more than three possible hormones; and the purely chromophobe adenomas, for reasons to follow, we may discard as having no secretory activity.

Adenomas of the ductless glands have long been known. To some of them processes of disease have been ascribed, but aside from the attribution of the acidophilic adenomas of the* pituitary body to acromegaly and of the so-called fetal adenomas of the ~~adenoma~~ to hyperthyroidism, they in the past have usually been regarded by pathologists as functionally inert conglomerations of cells of no particular consequence. But a revolution in this idea has come about through the recent disclosure that a tiny adenoma of a parathyroid glandule, of pancreatic islet tissue, or of the basophilic elements of the pituitary body, represents clusters of cells in an otherwise normal organ possessing a secretory potency and activity of astonishing degree.

In fact, the experimental reproduction of a hypersecretory syndrome by the successive daily injections of a glandular extract is a feeble imitation of the uninterrupted outpouring of an excess of the natural hormone from one of these hidden pathologic "stills." No moonshiner, with every effort to throw searchers off the track, ever ~~secreted~~ the spot where his demoralizing product was being distilled and prepared for distribution more skilfully than Nature has done in the case, for example, of that remarkable disease, deforming osteitis fibrosa, whose gross skeletal changes von Recklinghausen fully described over forty years ago in complete ignorance of their fountain-head.

thyroid /

uncelebrated /

1. THE CHROMOPHOBE ADENOMAS AND THEIR SYSTEMIC EFFECTS

To most of the known adenomas of the ductless glands, like those of the thyroid, parathyroids, pancreatic islets and adrenal cortex, a hypersecretory function is now ascribed. And this, as we shall see, is true also of the acidophilic and basophilic adenomas of the anterior pituitary, whereas the more common chromophobe adenomas, to which we may first turn, appear to be an exception to the rule.

Several histologic types of chromophobe adenomas have been described,^{11, 42} differing somewhat in their architecture and life history. All of them, however, are composed of cells having a nonstainable cytoplasm resembling the mother-cells, and not until

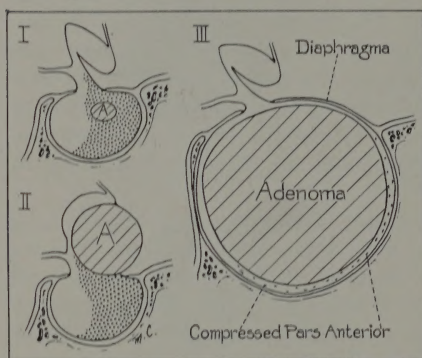


Fig. 2.—Diagrams of chromophobe adenomas (A) to show: *I*, small, nonsymptomatic lesion; *II*, a suprasellar lesion with chiasmal involvement but no secretory effect; *III*, an intrasellar lesion sparing chiasm but with dual hypopituitary effects from compression of glandular elements.

they reach a size sufficient to expand the membranous and bony envelope of the gland do they produce any recognizable constitutional disorder.⁶⁵ By this time the degree of intrasellar pressure has often become such that the residual of the normal gland is peripherally so thinned out the merest traces of it can be identified on histologic sections (cf. fig. 2 *III*). The symptomatic consequences of such a slow inactivation by compression are purely hypopituitary,

and the resultant adiposogenital dystrophy differs in no respect, except in its more insidious onset, from that which follows a subtotal hypophysectomy in the dog or rat, dwarfism being added to the picture if a preadolescent subject is the victim either of the disease or of the experiment.

Operations for these chromophobe adenomas are undertaken largely to preserve vision, for the expanding lesion stretches and distorts the overlying optic chiasm. And while this has no bearing on the present topic, what does pertain to it is the fact that after one of these soft expanding tumors has been radically excavated, the compressed normal elements of the gland may, in fortunate instances, resume their functional activity. This is shown, for example, by the occasional resump-

tion of normal menstruation in women previously amenorrheic, for which there can be no other ready explanation than the release of the sex-activating cells from their pressure inhibition.*

Fragments of a chromophobe adenoma, so far as I know, have been tested only twice by implantation methods to determine the presence or absence of an active hormone, with contradictory results.† There, however, is a further reason for believing that their clinical syndrome is not attributable to a secretory product. This is based on the complete absence of any recognizable symptoms except those of chiasmal involvement³⁶ when one of these tumors, owing to a defective diaphragma sellae, has escaped from its intrasellar confinement and come to lie in such a position that the activity of the rest of the gland continues unimpaired (cf. fig. 2 II).

While this argument may appear to have been unduly belabored, it seems necessary at the outset clearly to distinguish between the two actively secreting types of adenoma, subsequently to be considered, and these chromophobe tumors whose somatic effects, so far as one can determine, are purely hypopituitary.

Though the chromophobe adenomas are by far the most common type—the proportion in our series of 385 verified cases being 277 chromophobe, 107 acidophilic and "mixed," and 1 basophilic—the opportunity to study an early example post mortem has never arisen, and their more common point of origin is unknown. They vary considerably in their histologic appearance, some of them having an architecture suggesting an origin from the pars intermedia, others being structureless masses of cells in whose cytoplasm nonstainable granules suggesting secretory activity may sometimes be detected.

Whereas in the normal pituitary gland mitotic figures are not seen and are rarely if ever picked up in fixed and stained preparations of the adenomas, they occasionally may be detected on supravital preparations (cf. fig. 6). Nevertheless, these pituitary adenomas, while they may crowd their way into the cranial chamber and cause death, never seem to acquire malignant tendencies.

A few examples, possibly 2 per cent of the 385 cases, have been called adenocarcinoma by pathologists who have examined the tissues. But the fact that the patients from whom the specimens were taken, in spite of an incomplete removal of the lesion, have all survived the operation for many years belies the diagnosis of malignancy, and at the same time speaks in favor of their being composed of elements possessing no functional activity.

* That the adiposogenital symptoms brought about by these adenomas are not ascribable to involvement of the interbrain by the enlarging tumor is evident from the fact that an associated tuberal polyuria is exceedingly uncommon and is rarely elicited by the surgical manipulations necessary to expose and remove one of them. On the other hand, polyuria is a common feature of hypophysial duct tumors (craniopharyngiomas), the study of which led Erdheim to advance his hypothalamic explanation of the symptoms in Fröhlich's disease. And even should polyuria not have occurred spontaneously from the effects of a growth of this kind which is more apt to be suprasellar than intrasellar in position, it is almost certain to be produced by the operative manipulations necessary for its removal.

† Kraus alludes briefly⁷⁰ to his having observed on a single test a positive follicular effect. Berblinger,²² on the contrary, observed no effect on a single test.

Specimens removed at operation from a few of the tumors in our recent series have been studied by Dr. Severinghaus who finds: (1) that in the adenoma of acromegaly the Golgi body of all cells (fig. 3), whether chromophobe or acidophilic, is of acidophilic type; (2) that in the chromophobe adenomas the cells with a Golgi body of acidophilic type far outnumber those with a Golgi body of basophilic type. While no opportunity has arisen similarly to investigate a pure basophilic adenoma, it can readily be seen that these cytologic clues demand close pursuit.

Further studies in this direction may throw light on the composition of what Bailey and I have called ¹¹ "mixed" (chromophobe and acidophilic, never chromophobe and basophilic) adenomas, and may enable us to determine the nature of

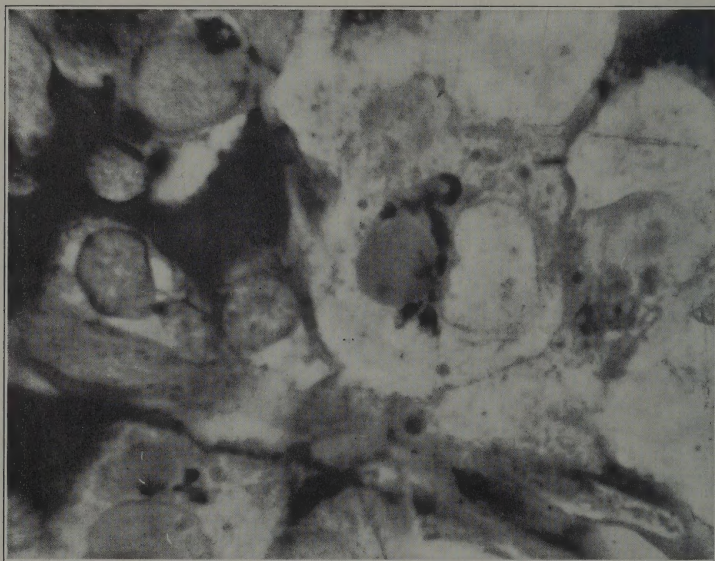


Fig. 3.—Photomicrograph of mixed adenoma (chromophobe and acidophilic) from case of "fugitive" acromegaly in which all elements have acidophilic type of Golgi net. Note large cell in center of field (magnification, $\times 2,400$).

the enlarged chromophobe elements characterizing the gland of pregnancy, which, because of their faintly acid-staining granules, many regard as arrested acidophils.

Chromophobe adenomas, while more commonly found in adults, occasionally occur in childhood under which circumstances their dual inhibitory effect on growth-promoting and sex-maturing elements is more clear. Such a case may now be cited for purposes of illustration:

THE CASE OF EVELYN D. (Surgical no. 22716). *A pituitary dwarf with combined intrasellar craniopharyngioma and chromophobe adenoma, twice operated on for neighborhood symptoms. Observed over a period of eight years. Recent intramuscular injections of a growth extract with symptomatic benefit but no acceleration of growth.*

Dec. 1, 1924: Admission of a 10 year old child (born Sept. 27, 1914), with headaches and impaired vision.

History.—At the age of 3, she had fallen from a piazza and cut her forehead, with no apparent ill effects. Apart from measles in her sixth year, she had been curiously exempt from the usual infections of childhood. She had been a bright and studious child who was disinclined to play with other children.

Present Illness.—A year prior to admission, she began to fall off noticeably in her school work. She was chided as being indolent, lazy and fat. Six months later, she began having troublesome headaches, became constipated and had

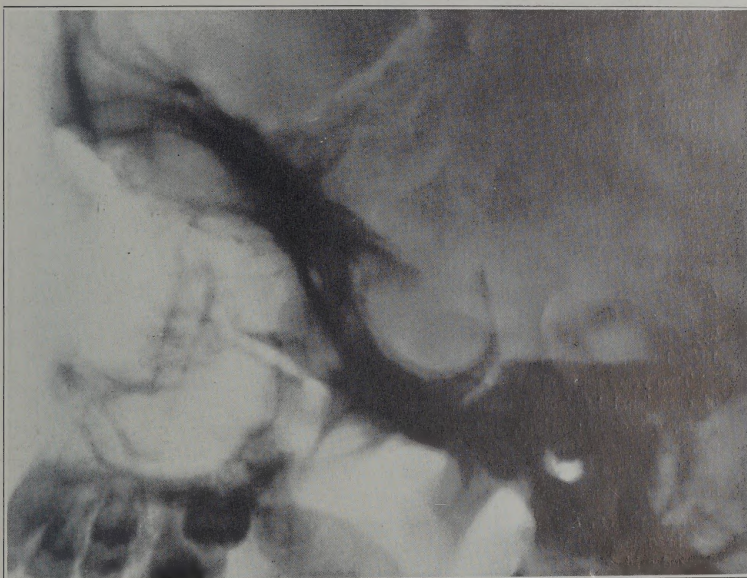


Fig. 4.—Expanded sella of Evelyn D. in 1924 (natural size).

attacks of vomiting. She grew sallow and lost weight in spite of her "puffy" appearance. Recently there had been a noticeable failure of eyesight.

Examination.—This showed a placid and cooperative child, definitely undersized but apparently well nourished; teeth very imperfect; height 3 feet 11½ inches (120 cm.; normal average for age, 131.5 cm.); weight 49 pounds (22.2 Kg.; normal average for age, 29 Kg.). The skin was delicate, pale and shiny suggesting a nephritic edema, but the urine was normal. The blood pressure was low, 85/45; the basal metabolic rate, —36 per cent.

The neurologic survey disclosed a bilateral primary optic atrophy more marked on the left where vision was reduced to the perception of movements. In the right eye there was 20/70 vision with an upper temporal field defect. Roentgenograms showed a highly ballooned sella without shadows of calcification either within or above the expanded fossa (fig. 4).

Clinical Diagnosis.—Owing to the rarity of pituitary adenomas of any kind in so young a child, the typical syndrome of Fröhlich was ascribed to a probable intrasellar, uncalcified hypophysial-duct (Rathke) tumor.

Operation, Dec. 19, 1924.—Ether anesthesia. A right transfrontal exploration disclosed a chiasm and optic nerves widely spread by a bulging though intact diaphragma sellae. Suspecting a cyst, a needle was introduced, and 10 cc. of a muddy, coffee-colored fluid containing cholesterol crystals was withdrawn. The collapsed diaphragma was then incised, and a glistening sheath of tissue 2 by 3 cm. in diameter representing the cyst wall was finally dissected out. This done, a mass of soft, brownish, adenomatous tissue was brought to view, and after specimens had been taken for histologic verification, the cavity was thoroughly cleaned out by suction.

The child made a good recovery from this operation (fig. 5). Headaches ceased; vision was subjectively improved, and perimetric tests on Jan. 1, 1925, showed definite widening of field peripheries. By January 10, the fields were normal in both eyes and the visual acuity 20/20 in each. The basal metabolic rate had risen twelve points, to —24 per cent. A series of x-ray treatments was given, and she was discharged Jan. 16, 1925, greatly improved in all respects.

The Tissues.—1. The cyst wall proved to be typical of an hypophysial duct lesion. 2. The adenoma was definitely of chromophobe type.

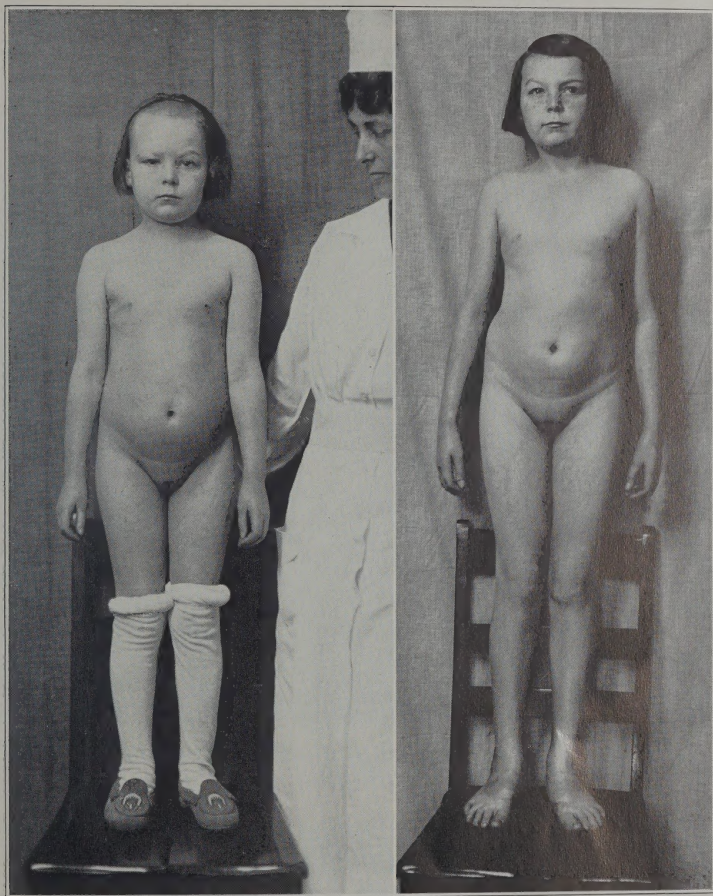
Subsequent Notes.—For the next twenty months, the patient was lost sight of, and in response to a letter of inquiry she finally reported on Oct. 16, 1926, at the age of 12 years and 1 month. Her height was then 127.2 cm., the increment of 7.9 cm. representing a slightly subnormal increase for a twenty month interval at her age (cf. fig. 10). She weighed 58½ pounds (26.5 Kg.), an increase of 9½ pounds (4.3 Kg.). The vision in the left eye, however, had fallen off to 10/200 with return of temporal hemianopsia and central scotoma.

Two years more elapsed when, on Jan. 26, 1929, she reported with the complaint of occasional headaches with beginning loss of vision in the left eye (aged 14 years, 4 months; height, 129 cm.; weight, 28.6 Kg.). During the next twelve months the symptoms slowly increased, and finally vision became so impaired she could make no further progress at school and her guardians were induced to have her reenter the hospital for further study.

Readmission, Jan. 30, 1930.—The child, as at the time of her first admission, had become apathetic, inactive and inclined to remain in bed. Both optic disks showed a high degree of atrophic pallor. The fields showed bitemporal hemianopsia more marked on the left, with macular involvement. Vision in the left eye was for movements only; in the right eye, 20/200. The child had grown 1.6 cm. in the preceding twelve months. The basal metabolic rate was —27 per cent. The sella was definitely enlarged over the previous entry.

Second Operation, Feb. 19, 1930.—Under procaine hydrochloride anesthesia, the original flap was reelevated, and the suprasellar region reexposed without difficulty. The diaphragma sellae had reformed and was bulging between the spread arms of the chiasm; it was electrically opened, and soft adenomatous tissue immediately began to extrude. After fragments had been secured for supravital study and for fixation, the cavity was once more thoroughly cleaned out, masses of the large tumor being easily dislodged by the spoon and removed by suction; no trace of the former cyst was seen. The margins of the incised diaphragma, having been drawn away from the nerves and chiasm until they rode free, were coagulated and infolded into the great cavity which would easily have held a large olive. After complete hemostasis, closure was carried out with the usual detail.

Postoperative Notes.—The child behaved admirably during the operation, and there was no reason to expect trouble. On the late afternoon of February 20 and again on the afternoon of February 22, the flap had to be reelevated for an



5/ Fig. 5.—Evelyn D. (standing on same chair). Left figure, shortly after first operation, Jan. 6, 1924, aged 10 years, 3 months. Right figure, Dec. 19, 1932, aged 18 years, 3 months.

extradural clot. There meanwhile was a marked hyperpyrexia (105 to 106 F.), which fortunately soon subsided. Though these unfortunate surgical complications delayed convalescence, her visual fields rapidly widened, and by March 10 acuity

was so far regained that she was able to read small print; the main object of the operation was therefore attained. By the time of her discharge, on May 4, 1930, while more alert than she had been on admission, she was pale and bloated and had little appetite for food.

Pathologic Note.—Supravital examination: The soft tumor was easily spread. The cells were typically of the large chromophobe type with delicately granular cytoplasm and large nuclei. Occasional multinuclear cells were seen and a single mitotic figure (fig. 6). Fixed sections showed a chromophobe adenoma with considerable intercellular fibrous tissue ascribed to the former operation. No further mitoses were found.

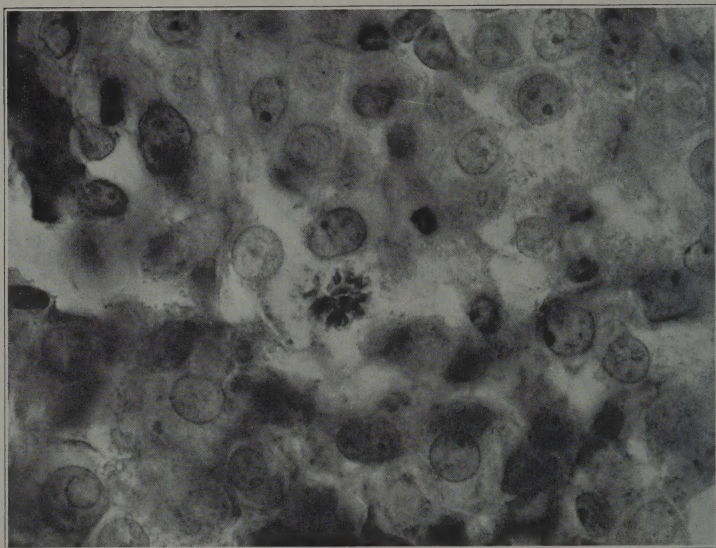


Fig. 6.—Supravital preparation of chromophobe adenoma from Evelyn D., showing mitotic figure (magnification $\times 850$).

Third Admission, June 13, 1931.—The patient reentered the hospital on request for the annual check on her condition. There had been little if any change. She was the same prim, laconic, undersized, well behaved child, with finely wrinkled and freckled skin (fig. 7). Her age was 16 years, 9 months; weight, 30.4 Kg.; height, 132.4 cm.—a gain of 1.4 cm. in sixteen months since the operation. The basal metabolic rate was -19 per cent. It had been our intention at this time to give her injections of a newly prepared growth extract, but its excess of protein content rendered this inadvisable.

Experiences with Replacement Therapy.—Obviously what this child needed from the first was some form of effective substitution therapy, and before continuing with her story, our ineffectual experiences in

this direction may be recounted. As already mentioned, the attempt had been made in 1909 to overcome the acute postoperative cachexia that commonly follows total hypophysectomy of adult dogs, and we had even reported⁸¹ what we thought were encouraging results following glandular implantations and the injections of crude bovine emulsions. Indeed, feeling that pituitary extracts might not be what is called species-specific, I had once transplanted the hypophysis taken from a still-born child into the brain of a man with an extreme degree of pituitary deficiency.



Fig. 7.—Evelyn D. at 18 years of age. Note persistent freckles on exposed areas of the otherwise pale skin, a characteristic of most hypopituitary cases.

This was done in accordance with Halsted's newly expressed formula⁶³ that glandular implantations would survive only in the presence of a physiologic deficit on the part of the host*; but the case, as it turned out, was highly unsuitable for such an experiment, the patient's critical symptoms (produced by a craniopharyngioma) having been hypothalamic rather than pituitary. The brain was selected as the

* These conclusions were based on experiences with parathyroid transplantations. Manley and Marine⁸⁷ showed a few years later that the parathyroid bodies readily survive autotransplantation in the absence of a physiologic deficit.

proper site for the transplantation on the assumption that the functioning gland required a neural environment.

Dr. Smith's subsequent success¹¹⁴ (1927) in restoring immature hypophysectomized rats to a normal status by daily intramuscular implantation of fresh glands was based on the principle of absorption of what active secretion was already present in the tissue, without expectation that the implant might survive to produce more, no evidence of this ever having been observed. While it may therefore be unavailing, further efforts to secure a functioning pituitary transplant will doubtless be made, for theoretically it would provide the ideal form of substitution.

We were made acquainted with some of Dr. Evans' early methods of preparing the growth hormone by one of his pupils, Mr. Harold Teel, who entered the Harvard Medical School in 1925. In collaboration with Dr. Tracy Putnam, a neutralized, dialyzed, potent and sterile extract was prepared,⁹⁸ armed with which we proceeded to elbow our way into the problem of experimental overgrowth. The prolonged intraperitoneal administration of the substance in dogs was found to cause what was looked on as the experimental counterpart of acromegaly.^{99, 17, 127}

Encouraged by the effectiveness on animals of this sterile extract, in May, 1927, Dr. Putnam gave seven successive intraperitoneal injections of 10 cc. of the substance to the minute pituitary dwarf described in another place³⁵ as an example of hypopituitarism due to a craniopharyngioma. Each injection caused a prompt evacuation of the bowels with vomiting, in spite of which they were continued over a week's time as they seemed definitely to improve the child's appetite and general condition. A temporary febrile reaction following the last injection, however, led to their discontinuance.

During the following year, Drs. Putnam and Teel¹²⁴ made some further improvements in their extract by salting out with sodium phosphate and succeeded in getting a potent substance which was not only sterile but reasonably free from protein. Meanwhile, much time was expended in searching for a suitable chemical assay of potency by the study of metabolism and other ways, the most promising being based on the finding by Teel and Watkins¹²⁸ of a definite drop of the non-protein nitrogen following injections of the hormone in dogs, suggesting "mobilization from the blood of substances needed for the building up of new protoplasm."

It soon proved to be beyond the capacity of our laboratory to prepare the extract in sufficient bulk for our purposes, and Parke, Davis and Company through the agency of Dr. E. P. Bugbee kindly agreed to come to our aid. They already had marketed an anterior lobe pituitary preparation (antuitrin) which one of my co-workers, Dr. Davidoff, had tested (1924-1925) in rats without being able to detect the presence of the growth hormone, the only observed effect being an interruption of estrus. Subsequently adopting the improved Putnam-Teel procedure with some modifications in the way of a preservative,²⁵ they have prepared a series of substances which are sterile, give no protein reaction on injection, and contain a sufficient amount of the growth hormone to give prompt effects when tested on hypophysectomized rats.

During the summer of 1929, one of the early preparations of modified anterior lobe pituitary preparation (antuitrin-G) was tested on three pituitary dwarfs ranging from the ages of 19 to 30, all with open

epiphyses. They received daily intragluteal injections of 5 cc. without appreciable effect; and on retesting the substance on rats, it was disappointingly found to have lost its growth-stimulating effect, possibly because of the nature of the preservative added to it. A more potent anterior lobe pituitary preparation which retained its activity was subsequently prepared, and to give this a reasonable trial Evelyn D. was readmitted to the hospital.

Fourth Admission, March 7, 1932.—During the twelve months' interval, normal vision had fortunately been retained, but the patient had lost ambition, spent most of her time in bed and was too indolent to go to school. This may in part have been due to consciousness of the increasing disparity between her age—she was now 17½—and her size. While her height (cf. fig. 10) had slowly increased (from 120 to 134 cm.) in the seven years she had been under observation and her weight had perceptibly jumped after each of the operations (cf. fig. 11), even this had remained stationary for eighteen months. Her epiphyses on x-ray films still resembled those of a child of 8 or 9 years. The blood pressure remained low, 90/60; also the basal metabolic rate, —18 per cent.

In view of the child's marked inappetence, preliminary studies were made of the calories she would normally consume on as appetizing a diet as could be provided; 964 calories was the highest she could be prevailed on to take. Meanwhile, the more potent anterior lobe pituitary preparation was tested intradermally and subcutaneously to exclude the possibility of a foreign protein reaction, and on March 16 she was given her first daily intramuscular injection of 2 cc. The effect on her appetite was immediate. Her measured calories on the second day were 1,285; on the third, 1,356; on the fourth, 1,466, and she was soon taking 1,600 calories *per diem*. Meanwhile, her appearance and activity were noticeably improved.*

The injections, which were continued for one hundred and ten days, were stepped up to 3 cc. on April 4 and to 4 cc. on May 20. She had by this time become so unusually alert and active she was a constant source of surprise to her relatives, and to keep her occupied she finally was given a position as a messenger girl in the ambulatory clinic.

She had gained in three months, from March 16 to June 28 when finally discharged, from 30.5 to 35.5 Kg., which almost equaled her gain (8 Kg.) during the preceding seven years. It was very difficult to be equally certain about her measured increase in height (from 134 to 135.5 cm.), for she stood more erect and variations of a centimeter or two occurred from day to day.

This, then, may be taken as a representative picture of dual hypopituitarism involving both factors of sex and growth; and the slow accession of growth the child has shown is ascribable to what remnants of the normal gland, relieved of pressure, have retained some degree of activity. Certainly the preparation of growth hormone, either from insufficient dosage, from too long delay in its administration or too short a time given to it, has shown no appreciable effects on the plotted graph

* Her blood studies, taken on March 8, had shown a nonprotein nitrogen of 15.07 mg. per hundred cubic centimeters, with a urine elimination for the twenty-four hours of 2.98 Gm. Corresponding studies made after the injections had been started showed a blood nonprotein nitrogen of 32.08 mg. per hundred cubic centimeters and a urine elimination of 5.56 Gm.

(cf. fig. 10). And though there was an acceleration of weight and a definite improvement in the child's general condition, her weight (cf. fig. 11) quickly dropped off on cessation of the treatment, in full conformity with what happens to laboratory animals when the daily administration of the growth hormone is interrupted.

The preparation of anterior lobe pituitary preparation which was employed was markedly potent when tested on a dwarf rat, whose weight had remained unchanged for more than a year after hypophysectomy. It, however, is obviously far from the ideal product necessary for effective substitutional therapy. Engelbach has recently (1932) reported⁴⁵ the case of a female pituitary dwarf 9 years of age who received over a period of eight and a half months subcutaneous injections of 9 cc. of a purified Evans growth hormone, during which period an increment of $2\frac{7}{10}$ inches (6.75 cm.) in height and a gain of $7\frac{1}{2}$ pounds (3.45 Kg.) in weight were recorded.

Reichert failed to observe¹⁰⁵ (1928) any effect on the growth of a puppy to which from the seventh to the eleventh month after hypophysectomy daily subcutaneous injections of the minced pituitary gland of a rabbit had been given. The only response was an imperfect sexual maturation with continued estrus; the failure to stimulate growth was ascribed to probable closure of the epiphyses. I, however, am informed by Dr. Evans that by the injection of 25 to 40 cc. daily of the more highly purified growth hormone he has recently described,⁴⁰ which is essentially free from the sex principle, it has been possible to bring about normal growth without acromegalic manifestations in a puppy hypophysectomized¹⁰⁶ by Dr. Reichert at eight weeks, treatment having been begun four weeks later.

While we may any day expect revelations in regard to this important matter of substitution therapy for dual hypopituitarism, the large amounts of the most effective known extract that must be intraperitoneally injected day after day effectively to compensate for the deficiency in experimental canine hypophysectomy precludes its clinical use; and the daily implantation of glands taken from the same species, so effective in dwarfed rats,¹¹⁴ is unfortunately inapplicable to human beings.

Growth and Sex.—Why should Nature have given to the pituitary body the control of two such important but, so far as can be seen, wholly unrelated activities as that pertaining to growth and that essential to reproduction, which more appropriately might have been controlled from a more caudal station? One would assume that they must somehow work together, for very similar nervous impulses must act on them, and the fact that adolescence normally occurs during a period of very rapid growth would suggest that they at least do not work in opposition as some of the early experiments with the injection of growth extracts had suggested.⁵² The therapeutic problem of the dwarfed child whose case has just been cited would have been simplified had the deprivation syndrome not been dual but consequent on the loss of either hormone by itself.

For want of any known agent capable of destroying or inactivating one type of secretory cell while the other is left intact, the possibility of studying by experiment the deprivation effects of either element singly is precluded. That such conditions, however, at least so far as the acidophils are concerned, may occur spontaneously has been shown by Smith and MacDowell,^{117, 118} who have made the surprising discovery that a defective gene has led to a congenital absence of acidophilic elements in the hypophysis of the hereditarily dwarfed mice of the Dunn strain. In these animals the growth principle alone is suppressed, leaving the gonadotropic hormone essentially unaffected else there could be no continuance of the species. Should it prove that all the elements of the adenohypophysis of these dwarfed mice possess a Golgi apparatus invariably of basophilic type, while that carrying the factor of growth to the acidophilic cells is lost, it will be of even greater interest from the standpoint of genetics. But even as they stand, these important observations indicate that the hormones of growth and sex have a separable rather than interdependent action.

Growth in the abstract is a highly mysterious process. It can unquestionably be checked by pituitary insufficiency, however brought about, or stimulated by administering the appropriate pituitary hormone. At the same time, it is well known that an inadequate diet and unhygienic surroundings may similarly impede a child's growth just as a change from unfavorable to more favorable surroundings where sunshine, fresh air and better food are plentiful may stimulate it. What if anything has the pituitary body to do with this? My friend, Dr. L. B. Mendel, a few years ago informed me that by an improved diet alone he could produce rats as large as those given pituitary injections, and suggested that the question be put to the test.

Accordingly, Drs. Bryan and Gaiser,²⁴ basing their study on the number of days required for 60 Gm. rats to attain a weight of 200 Gm., found that those on an ordinary diet for control purposes required an average of 50 days; those on Mendel's special growth diet required an average of 38 days; those on an ordinary diet supplemented by growth hormone required an average of 37 days; while those on Mendel's special diet supplemented by hormone injections required an average of only 28 days—a growth rate of 6 to 7 Gm. *per diem* which they regarded as the maximum attainable.

Polyphagia, as is well known, is a symptom of acromegaly; and dogs when injected with growth hormone become ravenous eaters. So, in the attempt to interpret these experiments, the question immediately arose as to whether the injections merely served to increase appetite or whether they actually stimulated growth by somehow making the nutriment more available as a building material.

We subsequently learned from Dr. Mendel that his co-workers, Anderson and Smith, had prepared a still more effective diet through which in the rat an average daily growth of 7.3 Gm. might be attained. And feeling that Dr. Mendel was not as yet convinced of the efficacy of the growth-promoting hormone by itself, we determined to see whether diet alone could effect the size of totally hypophysectomized rats whose weights never exceed that of the preoperative level. It was

found that the improved diet had no influence in starting growth. However, so soon as the administration of the growth hormone was begun, the animals promptly began to gain weight with a rapidity proportionate to the excellence of the different diets employed. On the other hand, cessation of the daily injections of the hormone was promptly followed by a loss of weight irrespective of the quality of the diet.

These experiments appeared to us to show the superiority of the hormone to diet as a growth-promoting influence, though they have left the question of appetite unanswered, for they were complicated and difficult enough to carry through without attempting to determine the precise number of calories the more rapidly growing rats consumed in comparison with those which grew more slowly.

It has been customary, as we have just seen, to measure the growth of four-footed laboratory animals in terms of weight, and the published graphs⁵³ consequently are difficult to transfer to the clinic with its plantigrade subjects whose measured erect height is the basis of registration. The closest parallel we have to what experimental gigantism in lower animals might be like if produced by a chemically pure hormone of growth is the exaggerated height occasionally attained by young persons in the period before epiphysial closure normally occurs. While it is not easy to determine just where overgrowth of this kind ceases to be merely excessive and becomes pathologic, I may cite two examples of patients at the present time under observation—both of them young normally adolescent lads, of whose rapid increase in stature records have fortunately been kept over a period of five to six years.

THE CASE OF JOHN J. This boy, now 16½ years of age, was born July 17, 1916, weighing 7½ pounds. As a child he was always considered to be somewhat undersized, but suddenly at the age of 8 he began to grow with unusual speed. Precise records unfortunately were not kept until two years later, but in the five years between March 26, 1927 (10 years, 8 months) and Jan. 2, 1932 (15 years, 6 months), he grew 36 cm. at the almost constant rate of something over 3 inches (7 cm.) a year.

When he first came under observation in September, 1931, he was found to be a normally proportioned, adolescent youth 6 feet, 4¾ inches (192 cm.) tall, and with a span 7 cm. greater than his height. His weight was 202 pounds (91.8 Kg.). Roentgenograms of the skull showed large accessory sinuses (fig. 8) and a suspiciously large sella which measured 14 by 17 cm. The long bones were normal in appearance with open epiphyses. His basal metabolic rate was normal. His blood pressure was 110/70.

No treatment was recommended, and the boy's parents were encouraged to look on the condition as indicating nothing abnormal. However, three months later, in January, 1932, he was brought in again because of the complaint of headaches and eye strain. What was taken to be early evidences of upper bitemporal defects in the visual fields were disclosed, and, fearing that after all he might conceivably have a pathologic hyperplasia of acidophilic elements, the pituitary gland was irradiated. During the next three months there was no measurable increment of growth when it again began to move up, and in July, 1932, the gland was again subjected to irradiation.

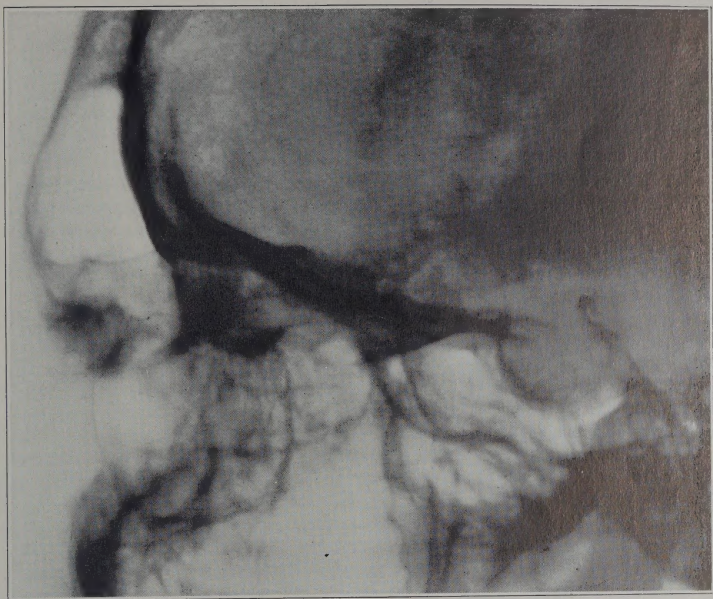


Fig. 8.—The slightly enlarged pituitary fossa in the case of John J. (natural size).

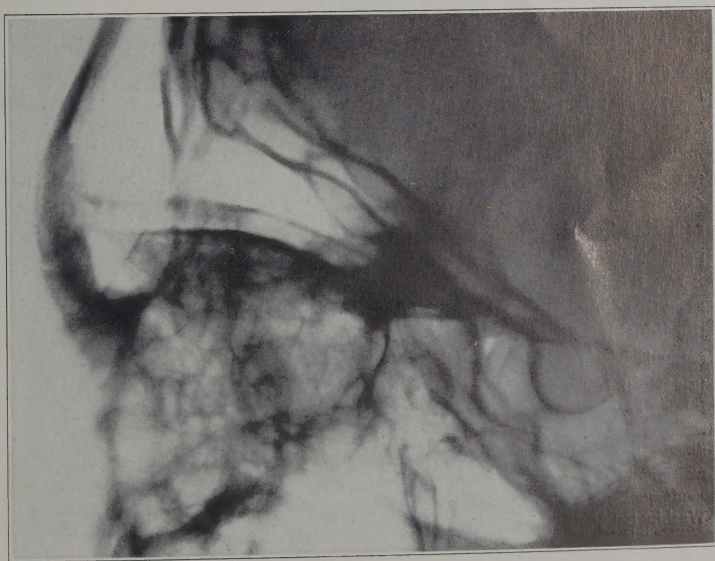


Fig. 9.—The small (for size of skull) pituitary fossa and large sinusoidal spaces in the case of Charles D. (natural size).

In the twelve months which have elapsed since the first of these radiotherapeutic sessions, there has been a growth of only five eighths of an inch instead of the yearly increment of 3 inches which his carefully plotted curve of growth would have led one to expect.

THE CASE OF CHARLES D. This boy, an orphan, born May 20, 1917, had been a frail and undersized child with a congenital dislocation of the lens in each eye, fortunately correctable by glasses. At the age of 7, he suddenly began to grow with great rapidity and when first seen, Oct. 17, 1927, at 10½ years of age, he was said to have grown 4 inches in the preceding twelve months and to have gained 60 pounds (27.2 Kg.) in weight.

He presented a not unfamiliar endocrinologic problem suggestive of adiposogenital dystrophy combined with overgrowth. Roentgenologic studies showed a disproportionately small sella (fig. 9), large accessory nasal sinuses, an area of calcification in the region of the pineal gland and normally open epiphyses. No treatment was recommended, and his guardians were advised to let him work out his own salvation. That he was genetically entitled to be tall was indicated by a family history of tall forebears on both sides of his family and by his having an elder brother who measured 6 feet, 2 inches in height and weighed 250 pounds.

Five years elapsed, when on Oct. 20, 1932, he again came under observation. He was then 15½ years of age, had passed through a normal adolescence, had lost his adiposity and become a spindling youth 6 feet, 7½ inches (201.8 cm.) tall. A careful record of his height and weight had fortunately been kept by his family physician, Dr. R. J. Carpenter, who during 1929 had found the boy to have glycosuria and low blood pressure (98/70), but these symptoms had spontaneously disappeared.

To see whether the excessive growth might be checked, as it appeared to have been in the preceding case, the hypophysis was irradiated under Dr. Sosman's direction six months ago. Since then, there has been no measurable increment in stature—a short time, to be sure.

On the accompanying graph (fig. 10), the growth of these lads has been carefully plotted with precise attention to the detail of the month of age at which the recorded measurements were taken, and the curve is a surprisingly regular one. It can be seen that their stature far exceeds the extreme upper limits of accepted heights for males of their age.* The x-ray treatments were given partly on the grounds that radiation is known to have a definitely inactivating effect on the growth-promoting adenoma of acromegaly, and partly because the prolonged x-ray treatment of a brain tumor of a young girl had inhibited her growth when compared with that of her identical twin sister. Whether the knuckle and plateau shown in the growth curve of these boys was caused by, or fortuitously coincided with, the radiation remains uncertain for want of such a control as would be deemed necessary in laboratory experimentation. The weight of John J. has not been taken

* The normal average height for males and females with the upper limit for males and lower limit for females in the shaded areas of the chart are plotted from Professor Bardeen's detailed figures recently prepared for the Child Conference in Washington.

with the same regularity as his height, but he had always been a normally proportioned youth with a proper height-weight ratio. Charles D., on the other hand, whose weight and height have always been taken together, has shown (cf. fig. 11) extraordinary fluctuations in weight as taken by different observers even though his progressive increment of height meanwhile remained unaffected.

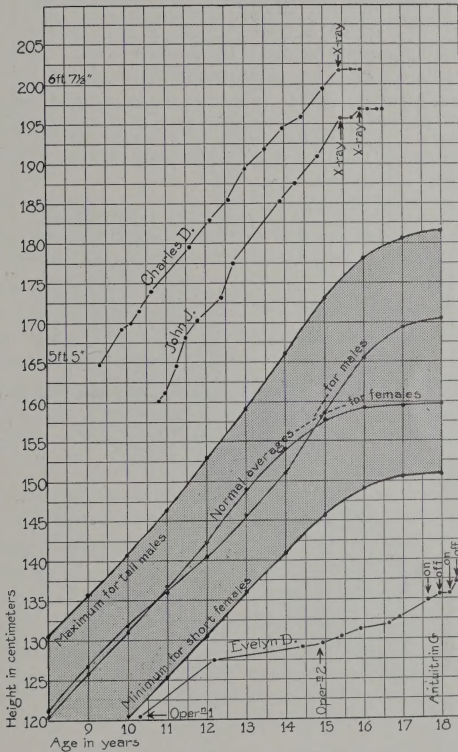


Fig. 10.—Height-age curves of Charles D., John J. and Evelyn D., compared with normal averages in shaded areas.

What, in terms of pituitary function, can be said of these overgrown 15 year old, normally adolescent boys? Are hereditary influences involved? Is their unusual height ascribable to a growth-stimulating diet with present-day attention to vitamins, or to an overactive pituitary gland, or possibly to the two in combination?

While precise figures are difficult to get at and properly to appraise when secured, it is a matter of common observation in recent years that children tend to be taller than their parents. Recalling that when I was a college undergraduate an anthropologically minded gymnasium director had annually made detailed measurements of all students—a custom which has since been continued—I have from this source obtained the comparative figures relating to the single factors of age and height of the present freshman class and that of forty years ago. Similar

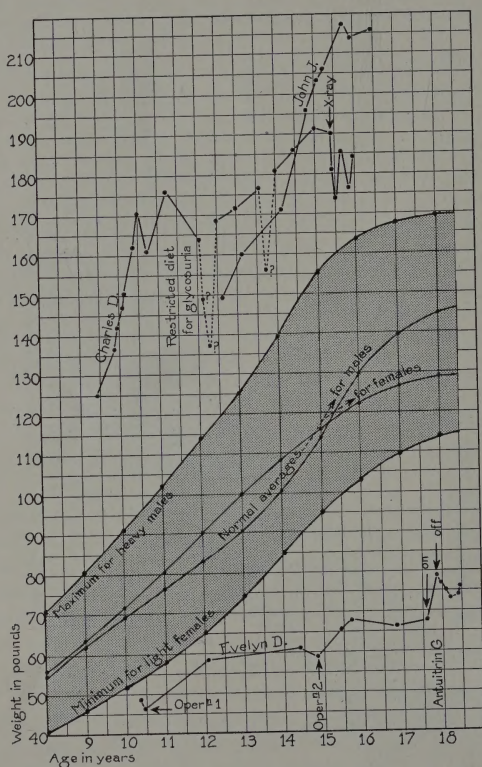


Fig. 11.—Weight-age curves of Charles D., John J. and Evelyn D., compared with normal averages in shaded areas.

figures have also been obtained from two other New England colleges. As it turns out, the average age (viz., $19\frac{1}{2}$) of freshmen in 1892 was a year older than that (viz., $18\frac{1}{2}$) of the freshmen in 1932, from which, all other things being equal, those of forty years ago should more nearly have attained their full stature.

The combined figures of the three institutions, however, show that only 5.67 per cent of the freshmen in 1892, in contrast to 19.47 per cent of the present, 1932, freshmen, were 6 feet or over. In other words, forty years ago *circa* one out of

every twenty matriculating students was 6 feet or over (the tallest 6 feet, 4 inches) whereas today *circa* one out of every five (the tallest 6 feet, 7 inches) is 6 feet or over.

2. THE ACIDOPHILIC ADENOMAS AND THEIR SYSTEMIC EFFECTS

Let us now turn to the consideration of pathologic overgrowth as represented in gigantism and acromegaly. Both conditions are now known to be associated with an adenoma the preponderance of whose elements in the active stage of the disorder show acidophilic granules.¹² This fact has provided the most dependable evidence at hand that the growth hormone actually is a product of these cells; and it is now made more certain by the recent disclosure I have mentioned¹¹⁷ regarding the absence of acidophilic elements in the pituitary glands of hereditarily dwarfed mice.

But if clinical gigantism and acromegaly are an unadulterated expression of overactive acidophilic elements resulting in an excess of growth hormone alone, why should these states so often be accompanied by dystrophic changes in the reproductive apparatus? It will be recalled that Evans' giant rats, and the acromegalic dogs produced in my laboratory, became not only overgrown but sexually dystrophic in the course of the experiment; but in neither laboratory was there then available a growth extract uncontaminated by the sex-maturing principle. And so far as the clinical disorders of like kind are concerned, reference has already been made to the fact that a growing adenoma composed of one type of cell may in time through compression destroy the functional activity of the remaining normal elements in the gland.⁶⁵

So for want of a simon-pure growth hormone, it is impossible to say with certainty whether excessive growth can be experimentally produced without associated gonadal effects. Nevertheless, what clinical evidence we have points in that direction. It is strongly suggested by the fact that in many acromegalics the evidences of sexual dysfunction are long delayed; and when the adenoma is too small really to expand the sella, there may, for example, in affected women be no interruption whatsoever of the normal menstrual cycle. Child-bearing, however, is apt to have a pronounced effect in activating the malady—an effect conceivably brought about by the increase of the growth hormone required for the needs of the child and acting at the same time deleteriously on the mother. In this connection, attention may be again called to the suspicion that the Erdheim-Stumme "pregnancy cells" are enlarged chromophobe elements arrested in the course of becoming fullblown granular acidophilic cells of usual type.

In the clinic we must take into account other factors than height and body weight when considering pathologic overgrowth. The acromegalic's stature may even become shorter owing to the immobility of

his thickening vertebrae, while at the same time he disproportionately gains weight. This in part is due to an increasing heaviness and solidity of the bones, in part to the peculiar "edema" of the connective tissues, but more particularly to the disproportionate increase in the size of the visceral organs.

To this feature of the disease—the splanchnomegaly—special attention was drawn in a report with L. M. Davidoff on the postmortem findings in four cases.⁴⁰ While it is not so apparent in experimentally induced overgrowth in the rat, splanchnomegaly in the dog after the prolonged administration of growth extracts may be extreme. Whereas the weight of one of our injected animals at the expiration of eighteen months was almost double that of the litter-mate control, the liver of the former was approximately three and one half times as large—an increment far greater than could be explained by the fatty infiltration and passive congestion that was present.

To what can this hypertrophy be ascribed? To an increase in the size of the cells or in their number within a given hepatic unit; or are the number of hepatic units actually increased? Or again, is the enlargement merely due to that sort of connective tissue thickening or edema which causes the puffiness of the cutaneous and subcutaneous tissues? To these questions there is as yet no wholly satisfactory answer.

It would be of little avail to include here the report of a typical case of acromegaly for its features are well known. It, however, is far from being a disorder which affects all its victims in the same way or in equal degree. The following case, which at the present writing is a source of anxiety, may serve as well as any other to show how complicated may be the syndrome and how great may be the difficulties of interpreting the secretory aspects of acidophilic hyperpituitarism in terms of experimental overgrowth in animals, particularly when they become masked and overlain by pressure involvement of the interbrain.

THE CASE OF MRS. E. L. (Surgical no. 27047). *Postpartum amenorrhea. Continued lactation. Fugitive acromegaly. Enlarged sella with neighborhood symptoms demanding operation. Chromophil adenoma. Subsequent pressure symptoms improved by irradiation. Ultimate symptomatic involvement of hypothalamus from intracranial expansion of tumor.*

Elizabeth L., born in 1893, with an excellent heredity and good general health, married a government official in 1917 when 24 years of age and went to Shanghai to live. She passed through her first pregnancy in 1919 without mishap. A second child, born a year and a half later (November, 1920), was similarly breast fed, but when weaned, at the expiration of twelve months, lactation continued in spite of all efforts to check it. Meanwhile, in the fourth month postpartum (March, 1921), normal menstruation had been resumed and continued for twelve months, when it ceased permanently.

In spite of the continued amenorrhea and persistent lactation, she regarded herself as well until November, 1925, when she began to have severe headaches with blurring of vision; and soon the sight in her right eye became seriously impaired.

Roentgenograms at this time disclosed an enlarged sella. At this juncture (December, 1925) a gynecologist explored the pelvis and, finding the ovaries in "a state of senile atrophy," split them sagittally and implanted under the peritoneum the supposedly normal ovaries from another patient.

On the patient's return to America for a visit the next year (1926), her parents were dismayed at her acromegalic appearance. She was still lactating profusely and troubled by excessive sweating. Not only had she gained some 40 pounds (18.1 Kg.) in weight, but she was distinctly exophthalmic, and her features had become coarse, hirsute and grossly enlarged with thick nose, lips and tongue. The ophthalmoscope disclosed a primary optic atrophy with definite haziness of the disk margins but no measurable swelling. Bitemporal field defects indicated

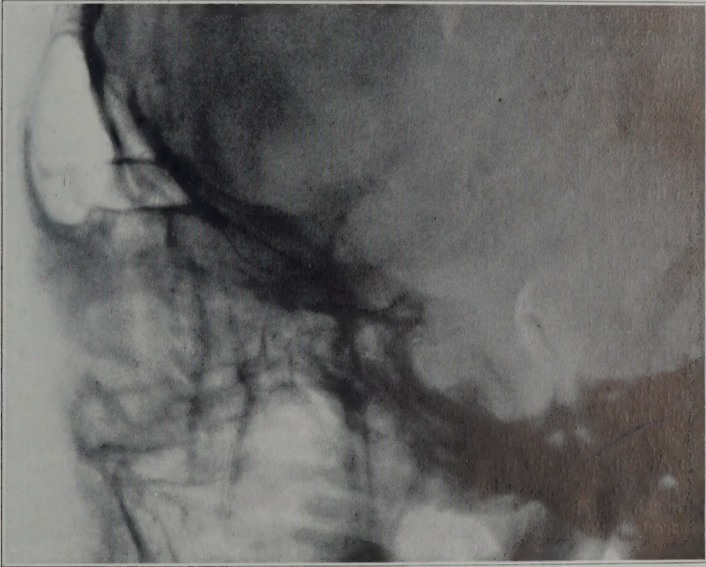


Fig. 12.—The ballooned sella in the case of "fugitive" acromegaly with prolonged lactation (natural size).

involvement of the chiasm by tumor; visual acuity in the right was reduced to appreciation of finger movements. Roentgenograms showed the phalangeal tufting characteristic of acromegaly and an expanded sella (fig. 12). The metabolism was —2; blood pressure, 110/65; height, 166 cm.; weight, 78.5 Kg.

To preserve vision, a transphenoidal operation (this being the procedure favored at the time) was performed (August, 1926), and as much as possible of the soft intrasellar growth was removed. The tissue showed cells of acidophilic type with alpha granules (Bailey) scattered among large chromophobe elements. From this operation the patient made a good recovery, with temporary cessation of headaches and improvement in vision. Active lactation, however, persisted, and she continued to gain weight, which by November reached 194 pounds (88 Kg.).

She reentered the hospital in February, 1927, because of a return of severe headache with occasional attacks of dizziness and projectile vomiting. Lactation and excessive sweating still persisted, and she at times was unduly somnolent. There was an unmistakable low grade of papilledema, particularly marked on the left. Her teeth which had become greatly decayed were extracted at this time at her insistence, and the pituitary region was thoroughly irradiated. This was followed by prompt subjective improvement and disappearance of the headache. There was a gradual diminution of lactation, which by November, 1927, had practically ceased; and though she had continued to gain weight up to 200 pounds (90.7 Kg.), her acromegalic appearance had noticeably lessened.

In February, 1928, her health was so greatly improved that she returned to Shanghai, and for the next eighteen months felt exceptionally well, though the amenorrhea persisted. In June, 1929, and again in September, 1929, she had a convulsive seizure with unconsciousness and incontinence of urine. In March, 1930, she began having peculiar momentary petit mal seizures with a "rush of blood to the head" and uncontrollable evacuation of the bladder. Apart from finding herself wet, the patient had no knowledge of these attacks and showed a curious disregard of them. Severe headaches from which she had been free for nearly three years again appeared with failing sight and hypersomnia. She was annoyed by a bruit synchronous with the pulse, which could be stopped by pressure on the neck. A series of x-ray treatments was given, and she was sent back to America, but before her arrival all these symptoms had disappeared, and there had been a marked improvement in vision.

On her readmission to the hospital (April, 1930) she was in good spirits, looked well and was symptom-free. Apart from haziness of the margins of the somewhat pale disks with measurable swelling of one diopter, the examination revealed nothing noteworthy. In June, 1930, she was given further roentgenotherapeutic treatments, and two months later she rejoined her husband in China. There for the next year and more she led an active life and felt reasonably well in spite of occasional petit mal seizures described as trances in which she would void involuntarily.

By January, 1932, the seizures began to grow more numerous and severe and in August, 1932, she returned again to America. On readmission to the hospital for study, she appeared in better general condition than at any previous time. Though still heavy (198 pounds [89.8 Kg.]), her acromegalic appearance was scarcely noticeable. The papilledema had disappeared; the visual fields were wide; visual acuity had improved. The blood pressure was 108/72; metabolism, — 11 per cent; there was no polydipsia or polyuria.

The peculiar attacks appeared to come in waves with intermissions of two or three weeks. They were characterized by a bright flush of face and neck with a profuse sweat and involuntary evacuation of the bladder. They so strongly suggested the autonomic (parasympathetic) stimulation brought about by hypothalamic irritation³⁷ it was finally decided to take ventriculograms. These were finally made (December, 1932) and showed a marked hydrocephalus with a filling defect of the third ventricle.

At this point, the story of the patient begins to get beyond the bounds of the present discourse. The prior history briefly summarized is that of a woman with mild acromegaly coming on after parturition with prolonged lactation, persistent amenorrhea and early evidences of intracranial pressure long unaccounted for and due, as finally shown,

to the suprasellar projection of an acidophilic adenoma into the third ventricle with resultant hydrocephalus and hypothalamic (autonomic) fits.

Fully to unravel the symptomatic effects of this lesion, while possible, is unnecessary here. There are, however, a few points to which special attention may be called:

1. The acromegalic symptoms of overgrowth shown by the patient were "fugitive"¹¹ and the adenoma, while acidophilic in type, was composed chiefly of large, undifferentiated chromophobe elements. It is not inconceivable that it may have been an adenoma arising from the "pregnancy cells" which, as already stated, may be chromophobe elements arrested in the process of ripening into acidophils. The human pituitary body of pregnancy, when transplanted into immature mice, has been shown by Philipp⁹⁵ to have temporarily lost its sex-maturing capacity, which would seem to indicate that the sex-maturing substances in the urine of pregnant women and in the placenta must come from some other source.

2. Whether the cells of the patient's tumor secreted a lactogenic hormone corresponding to the "prolactin" of Riddle¹⁰⁹ could only have been determined by testing the effect, on the previously sensitized mammary glands of animals, of implanted tissue taken from the growth. Both Riddle¹¹⁰ and Evans⁵³ feel assured that the adenohypophysis provides such a hormone definitely separable from the principles influencing growth and sex. If that is so, it was probably present (together with other impurities) in the early preparations of the growth hormone, for Putnam's acromegalic dogs showed hypertrophic, lactating mammae.* Conversely, Collip and his co-workers²⁸ have just shown that hypophysectomy of a rat after parturition leads to a prompt retrogression of the mammary glands with cessation of lactation.

3. In view of what is to follow in describing pituitary basophilism, it will be noted that the patient's blood pressure was invariably subnormal, which may in this case, as in chromophobe tumors, be ascribed to pressure obliteration of the neurohypophysis; and, similarly, her amenorrhea may be attributed to the compression effect of the large tumor on the cells (whatever they may be) that elaborate the luteinizing principle. The skin was pale, coarse, moist and without striae, and the adiposity was generally distributed and not confined to trunk and face.

4. The patient's periods of somnolence as well as the adiposity might conceivably be looked on as of hypothalamic origin, but both are frequently seen in cases of pituitary disease which does not involve the interbrain, and they were unassociated with polyuria. The temporary seizures appear to have been stimulatory episodes comparable to those described by Penfield⁹⁴ in the case of a patient with a proven third ventricle cyst.

3. BASOPHILIC ADENOMAS AND THEIR SYSTEMIC EFFECTS

So far, very little has been said of the hormone of sex other than that the mechanical effects of chromophobe adenomas of childhood produce a dual deficiency that inhibits both growth and maturation.

* This is not to be confused with the long known galactagogue effect of posterior lobe extracts.

For the same reason, the acidophilic adenoma of acromegaly may in time so compress the residual normal elements that sexual dysfunction is superimposed on the primary symptoms of overgrowth. This at least is the most probable explanation.

While evidence that the growth hormone comes from the acidophilic elements now appears to be conclusive, the attribution of the sex principle to the basophils is still under debate. There have been a few highly suggestive observations in its favor. One of them was the Smiths' ¹²⁰ demonstration (1923) that the central core of the bovine anterior lobe where basophilic cells abound possesses a greater sex-maturing potency than does the rim where acidophils predominate. Another was the identification by Addison ¹ of the so-called "castration cells" as basophilic elements. This in turn was followed by Engle's discovery ⁴⁶ (1929) that the gland of the castrated rat not only shows a multiplication of these elements but acquires increased potency as a sex-maturing agent, as shown by its effects when transplanted into immature mice.

This reciprocal reaction of Engle proves, however, not to be true of all species. Severinghaus ¹¹³ has shown, for example, that castration increases the sex-maturing capacity of the guinea-pig's hypophysis without demonstrable increase of the basophils. What is more, in man and some other mammalian forms, it is the acidophils that appear to be increased in castrates. On the other hand, it is said that in the rutting season and in animals (e. g., the marmot ^{101, 102}) emerging from hibernation, the number of basophilic cells are augmented; but in view of the known species variability and seasonal variation in the number of these elements, observations of this sort are difficult to appraise.

Furthermore, the quota of basophils is said to be greater than normal in certain clinical disorders, such as vascular hypertension and the uremic stage of renal disease, and I am inclined to believe that the same thing will be found true of eclampsia. More recently, Zondek has reported ¹³⁷ that the pars intermedia, pars nervosa and stalk of the human (but not of the bovine) hypophysis contains a follicle stimulating substance (prolan A) which he ascribes to the inwandering basophilic elements.

Now it has been recently brought to light that a well recognized polyglandular disorder—in the same sense, to be sure, that acromegaly is polyglandular—not infrequently is associated with a pure basophilic adenoma of the anterior pituitary.²⁸ Were it not that adenomas of this type have been thought to be exceedingly rare and of no pathologic significance, this disclosure would not have seemed so highly peculiar, and the patients with the disorder would continue as in the past to be looked on as the victims, for example, of osteomalacia, of hypertension or of diabetic obesity.

The external evidences of the disorder are unmistakable when once pointed out, and the accompanying photographs will show how rapidly it has developed in the course of a few months in the young girl, Alice D., 15 years of age, to whose case attention has elsewhere been

drawn.⁸⁹ The symptomatic features of the malady (not yet verified, to be sure in this particular instance) are subjoined:

There was a precocious adolescence, at 10 years of age, associated with normal menses which continued for three years and abruptly ceased. She acquired a peculiar plethoric appearance with an abnormal growth of hair on brows, lip and chin (fig. 13). She became increasingly abdominous with progressive increase of purplish striae atrophicae (fig. 14).

She has had persistent backache and become round shouldered with the loss of 4 cm. in measured stature, due undoubtedly to the roentgenologically evident decalcification of the vertebrae and an abnormally high calcium elimination. A spontaneous fracture of the pelvic bone, evidently in a tumor, has healed with callus formation.



Fig. 13.—Facial hirsuties in a case of pituitary basophilism at 15 years of age.

She has a subnormal basal metabolic rate, a lowered tolerance for carbohydrates and a high blood pressure, presumably indicating secondary involvement or imbalance of other glands — parathyroid, thyroid, pancreatic islets and adrenal—to almost any one of which the syndrome might have been ascribed.

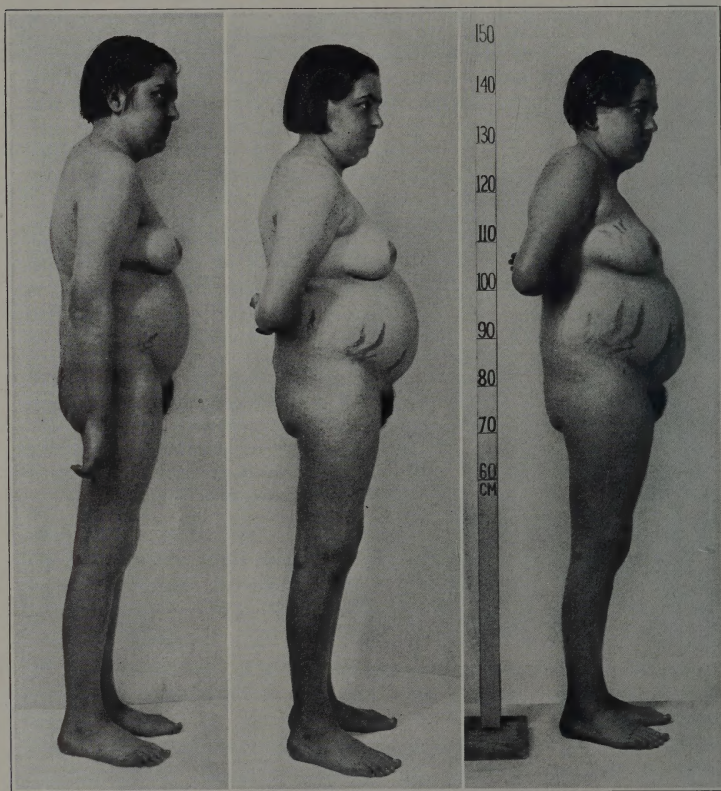
Her urine tested by two observers on both rabbits and immature mice proved to contain a follicular-stimulating substance indistinguishable in its effects from prolactin A (rho I).*

While from case to case, as is true of acromegaly, the syndrome varies considerably, its frequent association with a basophilic adenoma of the hypophysis must be something more than accidental. The disorder proves

to be not uncommon, and suggestive clinical examples are found scattered in the literature dealing primarily with osteomalacia,⁸⁹ hypertension,⁹² adiposity¹⁰⁰ and dermatologic topics,⁶⁶ or merely reported

* In April, 1932, and again in June and August, she was given a series of deep x-ray treatments directed toward the pituitary body. There was an early relief of backache. In August, a definite diminution of the facial hirsutism was noted. By September, her blood pressure, originally averaging 140/105, had dropped to 115/80 and has remained there. In October, the abdominal striae began to lose their bright color. In February, 1933, a normal menstrual period occurred after two years and ten months of amenorrhea with disappearance from the urine of the follicle-stimulating substance.

as an instance of a remarkable disease.¹⁰⁷ In a recent tabulation by Mr. Henderson of the symptoms shown by the patients in our series with hypopituitarism due to chromophobe adenomas (verified or suspected), two of the patients were found to have an elevated blood pressure, and a review of their case histories makes it now obvious



April, 1932

July, 1932

October, 1932

Fig. 14.—Progress of acute pituitary basophilism (unverified) in six months period.

that they were probably victims of basophilism. Indeed, an unmistakable case (that of Theresa L., cf. fig. 15) has come to light while reviewing, for the purposes of this paper, the polyglandular changes found in the seventeen patients that died after operation for what was formerly diagnosed and indexed in the files as a chromophobe adenoma.

Since hyperadrenalism and possibly other endocrine derangements may provoke a somewhat similar syndrome, it is unsafe as yet to pin too much faith on clinical symptoms alone, and only those examples of the disorder in which a postmortem examination has been held are dependable. Records are at hand of seventeen cases that came to autopsy,* in fourteen of which the condition has been shown to be associated with pituitary adenomas. In two of the three negative cases,^{132, 90} the



Fig. 15.—Miss L. Facial hirsutism with verified pituitary adenoma (? basophilic) invading cranial chamber.

gland was said to have been normal without further specification; in the third, the Leyton-Turnbull-Bratton case⁸³ (in regard to which I over-reached myself in predicting³⁷ that a basophilic adenoma would be found), no lesion has been detected on recent serial sections

* My attention has been called by Professor Günther of Leipzig to another unmistakable case with a proved basophilic adenoma reported by Drs. Theodor Bauer and Hans Wassing (Zur Frage der Adipositas hypophysarea: Basophiles Adenom der Hypophyse, Wien. klin. Wchnschr. **26**:1236-1243, 1913).

of the gland. Of the fourteen cases actually associated with a pituitary adenoma, in three instances it was a large, unclassifiable growth, only fragments of which were examined, whereas in the other eleven it was a small, circumscribed, typically basophilic lesion.

For the purpose of showing the principal symptomatic and pathologic features of the fourteen cases with verified adenomas, the data,

Verified Pituitary Adenomas Causing Syndrome of Basophilism,

Number	Case	Date of Report	Sex*	Age		Type of Adenoma Weight of Hypophysis	Principal Symptoms								
				Onset	Death		Abdominal Obesity	Amenorrhea	Hirsutism	Abdominal Striae	Glycosuria	Metabolic Rate (Basal)	Hypertension	Skeletal Decalcification	
1	Schmorl ¹¹¹ -Mollneus ⁸⁹	1913	♀	20	48	Large basophil	Yes	Yes	Yes +					Fracture	
2	Anderson's ⁸	1915	♀	21	26	Basophil	Yes	Yes	Yes	Yes			+ 185	Fractures	
3	Reichmann's ¹⁰⁷	1919	♀	15?	36	"Eosinophilic"?	Face only	Yes	Yes				++ 210	Yes marked	
4	Zondek's ¹³⁰	1923	♀	19	24	? Small	Yes	Yes	Yes	Yes +	Yes			Yes	
5	Raab ¹⁰⁰ -Kraus ⁷⁰	1924	♂	?	31	Basophil 93 mg.	Yes	Impotence	None	Yes ++	Yes			Yes	
6	Parkes Weber's ⁹⁸	1926	♀	23	28	Basophil	Yes	Yes		Yes ++		+20	++ 230		
7	Bauer's ¹⁴	1930	♀	34	36	Basophil	Yes	Yes	Yes ++	Yes	Yes	+28	+185	Suggestive x-ray	
8	Wieth-Pedersen's ¹³⁸ ...	1931	♂	20	24	?	Yes	Impotence	None	Yes ++	Yes	Normal	+190		
9	Teel's ¹²⁰	1931	♀	15	20	Basophil	Yes	?	Yes			+33			
10	Moehlig's ⁸⁸	1932	♀	34	43	Basophil	Yes	Castrate	Yes	Yes		+31 -1	++ 230		
11	Bishop-Close ²³	1932	♀	15	22	Basophil	Yes	Yes	Yes ++		Yes		++ 250	Fracture	
12	Berblinger's ²²	1932	♀	?	?	Basophil	None	Castrate +	Yes +	Yes				Yes	
13	Miss L No. 14327.....	1921	♀	18	45	Large invasive	Yes	Yes	Yes +	Yes	Yes	-4	+170		
14	Miss P No. 42211.....	1932	♀	20	33	Basophil 71 mg.	Face chiefly	Yes	Yes ++	Yes ++	Yes	-40 -1	++ 240	Fractures	

* ♀ indicates female; ♂, male.

so far as the fragmentary protocols which accompany many of the reports permit, have been assembled in the accompanying table.* To a detailed consideration of the last of these cases we may now turn. As will be told, I had seen the patient briefly in consultation twelve

* Attention may be drawn to the number of patients that died from acute pulmonary complications ascribed to edema.

years ago and not again until she was recently referred to the hospital by Dr. Goodale of Boston as ~~having~~ a case of probable pituitary basophilism.

THE CASE OF MISS P. (Surgical no. 42211). Onset of amenorrhea with plethoric adiposity, purple striae atrophicae and hypertension at 19 years of age. Relative subsidence of symptoms for ten years followed by exacerbation. Multiple fractures,

with Principal Symptoms and Ductless-Gland Changes as Recorded

Postmortem Findings								
Thyroid and Cells	Parathyroids	Thymus	Pancreas Islets	Hypertrophic Adrenal Cortex	Gonads	Arteriosclerosis	Osteomalacia	Cause of Death
Colloid goiter	Large adenoma?		Fatty		Atrophic		Brown tumors ++	?
Slightly enlarged	"Normal"	Atrophic		Yes	"Senile"	Yes	"Brittle bones"	Asthenia
Small; low cuboidal		Not identified	Normal	Yes 8.5-15 Gm.	Atretic; no corpora	Yes +	?	Following adrenalectomy
Small	?	Atrophic	Fatty		Follicular atresia		Yes ++	Erysipelas
Slightly enlarged	Large fatty 0.16 Gm.		94 Gm.	?	18.3 Gm.; no spermatozoa		Yes ++	Sepsis
"Size walnut"		"Chiefly fat"		Yes 11-9 Gm.	Atretic; no corpora	Yes	?	Pulmonary edema
Small; low cuboidal			Normal	None	Follicular; no corpora	Yes	?	Following adrenalectomy
Small			Normal	Yes				Respiratory dyspnea
Slightly enlarged		"Persistent"	Slightly enlarged	Yes	1 corpus luteum			Meningitis
Autopsy restricted to brain								Following thyroidectomy
Low cuboidal					Atretic; no corpora	Yes		Pulmonary edema
.....				Yes	Castrate		Yes "senile"	?
Small 11.5 Gm.	Large fatty 0.1 Gm.	Not identified	90 Gm. fatty	Yes 9-10 Gm.	Atretic; no corpora	None (?)		Pituitary operation
Small 15 Gm.	Large fatty	Atrophic	Fatty	Yes	Atretic; no corpora	Yes ++	Yes, slight	Pulmonary edema

glycosuria and hypertension. Death from acute pulmonary complications. Postmortem examination. Basophilic adenoma; hypertrophic adrenal glands; extreme atherosclerosis.

Oct. 24, 1932: Admission of Miss P., 33 years of age.

Past History.—Born of healthy parents with an untainted family history, she, as a child, in addition to frequent "colds," had had measles, mumps, whooping cough, chickenpox and an attack of erysipelas; in 1908, an emergency appendectomy had been performed. She attained a normal adolescence when 13 and grew

into an intelligent, vigorous and ambitious young woman. She entered college at 18, but became unhappy there and withdrew at the end of her second year. This determination she ascribes to restlessness, for she believes herself to have been "nervous, irritable, tense and emotionally unstable as long as she can remember." Because of her round face, she had been nicknamed "moony."

Present Illness.—Her want of success at college may have been due to physical rather than temperamental causes. It at least coincided with the symptomatic onset of her malady, for in June, 1919, she ceased to menstruate, and subsequently while at a summer camp she developed a ravenous appetite. Always unduly fond of sweets, she began rapidly to gain weight, particularly noticeable in the face and abdomen. She became "gross, florid and bloated about the eyes (piggy-eyed)." During the summer she broke her ankle. Purplish striae of the body and arms began to appear at this time, and she has never since ventured to wear a sleeveless dress. In December, 1919, she found herself easily fatigued and acquired a definite polyuria and polydipsia. At the same time she began having headaches with blurred vision, tinnitus, dizziness and numbness of the hands.

Toward the end of February, 1920, because of a sudden fainting attack she came under the care of Dr. E. P. Joslin who found she had a moderate hyperglycemia with glycosuria and a basal metabolic rate of — 30 per cent. The puffy appearance of her eyes and face, dry skin, marked supraclavicular fat pads, and her complaint of being mentally sluggish strongly suggested myxedema.

On March 13, 1920, she was first briefly seen in consultation with Dr. Joslin. Her facial hypertrichosis and the peculiar disposition of the adiposity with extraordinarily widespread striae atrophicae associated with a moderate hypertension (140/100) indicated a polyglandular syndrome recognized as resembling that in the case of "Minnie G." ³⁸ No therapeutic suggestions were made.

By January, 1921, she had become increasingly hirsute and "bloated," and at this juncture she came under the care of Dr. Timme at the Neurological Institute in New York. There she was given salt baths, graded exercises and various glandular preparations, including lutein, thyroid and pituitary. After four weeks' treatment, her weight was greatly reduced, the hirsuties had disappeared, and normal menstruation was resumed. From this time for a period of five years, she continued under various combinations of glandular treatment and regarded herself as reasonably well.

In 1926, her face again began to get heavily bearded and after trying various forms of proprietary treatment, she finally resorted to the daily use of a razor. In May, 1927, her adenoids, tonsils and impacted wisdom teeth were removed, and it was noted by the attendant that her blood pressure was high (155/115). In 1929, she had a "nervous breakdown." During March, 1930, she was elaborately studied at the Evans Memorial Hospital. At this time, the urine showed some albumin and occasional hyaline casts with normal phthalein test. She had a low sugar tolerance, a fluctuating hypertension, basal metabolic rate of — 14 per cent and a cardiac enlargement. The possibility of hyperthyroidism, virilism, primary ovarian disorder and myxedema was discussed. She was subsequently under observation at the Lahey Clinic as presenting a possible thyroid problem.

In January, 1931, the menstrual periods, after having been essentially regular for ten years, again ceased. In July, 1931, she was found to have a marked hypertension, from 220 to 250 systolic. She nevertheless passed the summer of this year with Grenfell in Labrador and enjoyed her work there.

In April, 1932, she fell and broke her humerus. During the following summer she became conscious of a change in disposition. She began to complain of polydipsia, occipital headaches, palpitation, shortness of breath, and swelling of feet and ankles. The fatness of face and shoulders, dryness and pigmentation of the skin,

cyanosis of dependent hands and feet had markedly increased. She observed that large ecchymoses would follow the slightest bruise and that a cut or scratch would bleed excessively. At this juncture, in October, 1932, she was referred to the Brigham Hospital for study.

Physical Examination.—The patient was a rather tall woman, 5 feet, 9½ inches (175.8 cm.), weighing 63.5 Kg., with a peculiar moon-shaped, recently shaven face and clipped eyebrows. The eyes were puffy; there were posterior cervical and supraclavicular fat pads. She was not appreciably round shouldered other than



Fig. 16.—Striae atrophicae of arm, axilla and breast.

the cervical fat pad would account for. Though not particularly abdominous, the parietes were somewhat pendulous and flabby. The extremities did not participate in the adiposity. Over arms, axillae, breasts, abdomen, hips, groins and thighs were an extraordinary number of broad, pale striae atrophicae which deepened in color on slight rubbing (fig. 16). The lower extremities showed marked pigmentation and scarring of the dry and scaly skin with several large fading ecchymoses from recent trivial contusions.

The blood pressure averaged 220/170; the urine showed a trace of sugar and of albumin with no renal elements. There was a variable polyuria amounting to *circa* 3 liters. The basal metabolic rate was — 10 per cent. The detailed blood exami-

nation showed 4,720,000 erythrocytes with hemoglobin (Sahli) of 106 per cent = 14.63 Gm. The nonprotein nitrogen was 46.97 mg. per cent and the cholesterol 192.3 mg. per cent; all other chemical tests being within normal limits.

Roentgenograms showed (Dr. M. C. Sosman) "a slight diffuse atrophy of the vertebral bodies without collapse or deformity; normal detail of the cranial bones; a sella of normal dimensions (fig. 17) but hazy outline. Multiple small tiny shadows in both flanks suggesting renal calculi—a common finding in hyperparathyroidism."

The patient was transferred to the Huntington Hospital where, through the kindness of Dr. J. C. Aub, her elimination was thoroughly studied. He reported essentially normal blood content for calcium phosphorus and phosphatase and a



Fig. 17.—Sella of normal configuration but hazy outline from decalcification in case of Miss P.

normal elimination of both calcium and phosphorus. She showed a low sugar tolerance and a high nitrogen output,* as shown by an average loss of 6.7 Gm. daily on a balanced diet containing 56 Gm. of protein.†

* This condition of "azoturia" (Woodyatt) was also observed in another example of the disease (case 11) in a former report.³⁸ In acromegaly, on the contrary, there appears to be a prompt utilization of nonprotein nitrogen.¹²⁸

† Biologic tests of the patient's urine at this time were made by Dr. Fuller Albright who found on tests with rats no follicular-stimulating substance (rho I) such as had been found in the urine of Alice D. when tested on rabbits. This effect would normally be expected on the basis of Zondek's¹³⁶ explanation of amenorrhea as conditioned by the overproduction of the follicularizing hormone.

On her readmission to the Brigham Hospital, the pituitary body was irradiated on four successive days without immediate effects of any appreciable kind. She was discharged Nov. 12, 1932. She returned to her home and resumed her usual activities. On the night of December 3, she had been to the theater, and though complaining of fatigue, she nevertheless joined a supper party and retired about midnight. An hour later, she awoke with dyspnea, became increasingly cyanosed, and died twelve hours later from what was supposed to be acute pulmonary edema.

Autopsy (Drs. R. Z. Schulz, George Hass and author).—Forty-eight hours had elapsed before news of her death was received and an autopsy could be solicited and performed. The body had fortunately been well embalmed. The general condition, in brief, showed marked adiposity, particularly abdominal and mediastinal. There was no splanchnomegaly or apparent anomaly of the liver (1,740 Gm.), spleen



Fig. 18.—Marked atherosclerosis of aorta (natural size).

(100 Gm.) or pancreas (65 Gm.). The kidneys (170 and 175 Gm.) had slightly adherent capsules, and on section numerous minute brownish calculi were visible in the calices of the pelves. The heart was enlarged (695 Gm.), and the lungs (720 and 620 Gm.) showed merely a few patches of congestion. There was an advanced degree of atherosclerosis chiefly apparent in the aorta and larger arteries. The bones, particularly the vertebral bodies, were easily cut with a knife, suggesting osteoporosis, but the tissue showed no gross change.

The histologic study of these organs and tissues principally showed: (1) a chronic vascular nephritis, with sclerosed glomeruli and calcific deposits; (2) hypertrophy of the cardiac musculature; (3) apart from the arterial changes, an essentially normal structure of spleen, liver and pancreas; (4) an acute bronchitis and bronchopneumonia. The bones showed definite osteomalacia. The Paneth cells of the intestine were noted as being particularly prominent. A section of one of the cutaneous striae showed obliteration of the papillae of the corium with swollen and fragmented elastic fibrils. There was marked atheromatous degeneration of the aorta (fig. 18) and large arteries.

The Endocrine Organs.—The adrenal glands (fig. 19) were hypertrophic; the left (14 Gm.) measured 8 by 3 cm.; the right (12 Gm.) measured 7 by 4 cm. and showed possible small adenomas on fresh section. A small nodule of adrenal tissue was identified in the stalk of the ovary. The heavy yellow cortical layer of each gland measured 2 mm. in thickness. The evident hyperplasia was found histologically to be restricted to the zona fasciculata (cf. fig. 31) whose cells were distended with lipid material.

No thymic tissue could be definitely identified in the mass of mediastinal fat, but an area of suspicious tissue was removed for study. Sections show only a few atrophic epithelial cords of thymic tissue, no Hassall's corpuscles being found.



Fig. 19.—Cleanly dissected adrenal glands: left, 14 Gm.; right, 12 Gm. (natural size). (Cf. fig. 31.)

The thyroid gland (fig. 20) was small (15.1 Gm.). The parenchyma was composed of closely packed, rather small acini containing deeply-staining colloid. There were no papillary infoldings and the cells were of a low cuboidal type.

Four parathyroid glandules were identified, two of them slightly enlarged, measuring, respectively, 7 by 5 by 2 and 10 by 5 by 3 mm. in diameter. Histologic study of the larger of them showed an essentially normal appearance apart from the fact that approximately two thirds of the volume of the gland was composed of fat. The cells are of the pale variety with a few scattered acidophilic elements and occasional droplets of colloid.

The pancreatic islets are numerous and appear to be normal in their structure.

The uterus, tubes and ovaries together (fig. 21) weighed 65 Gm. The uterus was small, acutely retroflexed, and the endometrial as well as the cervical glands



Fig. 20.—The 15 Gm. thyroid gland (natural size) with adherent parathyroids.



Fig. 21.—Uterus, tubes and ovaries (slightly reduced) ; weight, 65 Gm.

were found to be uniformly atrophic. The right ovary measured 40 by 25 by 20 mm. and contained a superficially placed thin-walled cyst measuring approximately 25 mm. in diameter. The left ovary measured 30 by 12 by 15 mm. and showed no superficial cysts, but on fresh section numerous small cystic areas were apparent. Microscopically, the ovaries are found to have an essentially normal stroma in which a few large corpora albicantia and numerous follicular cysts of variable size are embedded (cf. figs. 33 and 34). The germinal epithelium is tall and columnar in type and does not appear to be abnormal; numerous primordial ova are to be seen. The cystic follicles are lined by atretic granulosa cells showing mitoses, in some of them a cumulus containing an atretic oocyte being discernible. The theca interna is well vascularized, cellular, both mitotic and pseudomitotic figures being numerous.

The Pituitary Body.—Since it is with the hypophysis in this case that we are chiefly concerned, it deserves more detailed consideration. When the brain had been removed leaving the sella exposed, the diaphragma was found to be defective leaving exposed the larger portion of the upper surface of a nonprotruding hypophysis with its attached stalk. On carefully removing the gland (fig. 22), it proved to be small (71 mg.) and of normal appearance. Scarcely hoping to find the predicted lesion, the organ after fixation was serially cut in coronal sections.



Fig. 22.—Upper surface of pituitary body (natural size); weight, 74 mg.

Three of these sections are shown in low magnification in the accompanying photomicrographs (fig. 23 *A*, *B* and *C*). The first of them (*A*) passes through the largest diameter of a lateral and anteriorly situated oval adenoma of pure basophilic type (cf. figs. 24 and 25) measuring 7 by 2.5 mm.

The second section (fig. 23*B*) through the center of the gland transects the anterior part of the neurohypophysis and shows the marked invasion of the lobe by inwandering basophilic elements (cf. fig. 26). These invading cells, either by a holocrine or apocrine method of secretion, appear to disgorge their granular cytoplasm, masses of which are not only to be seen in the vicinity of the more deeply invading

cells (fig. 27) but can be traced into the loose tissue of stalk and tuber from which region, however, the soluble substance has largely been dissolved out (?) in process of fixation of the tissues.

The third section (fig. 23*C*) transects both neurohypophysis and stalk and shows (to the right side) a part of the anterior lobe in which acidophilic and basophilic elements are present in normal proportions. In this section only a small crescent of the highly vascularized tuberal cuff of the adenohypophysis remains apparent on the anterior (upper) surface of the transected stalk, whereas in figure 23*B* it completely surrounds the stalk. Due possibly to the patient's extreme cyanosis at the time of death, the "portal system" (Popa and Fielding;⁶⁷ Basir¹³) of diencephalo-hypophysial veins which passed through the stalk was greatly engorged (fig. 28). On high power magnification, some of the communicating vessels of this system prove to be filled, almost to the exclusion of erythrocytes, with what appears to be granular secretion (fig. 29). Clumps of the same appearing substance are to be seen here and there in the loose meshed glia of the neurohypophysis and can be traced even into the stalk and region of the tuberal nuclei.

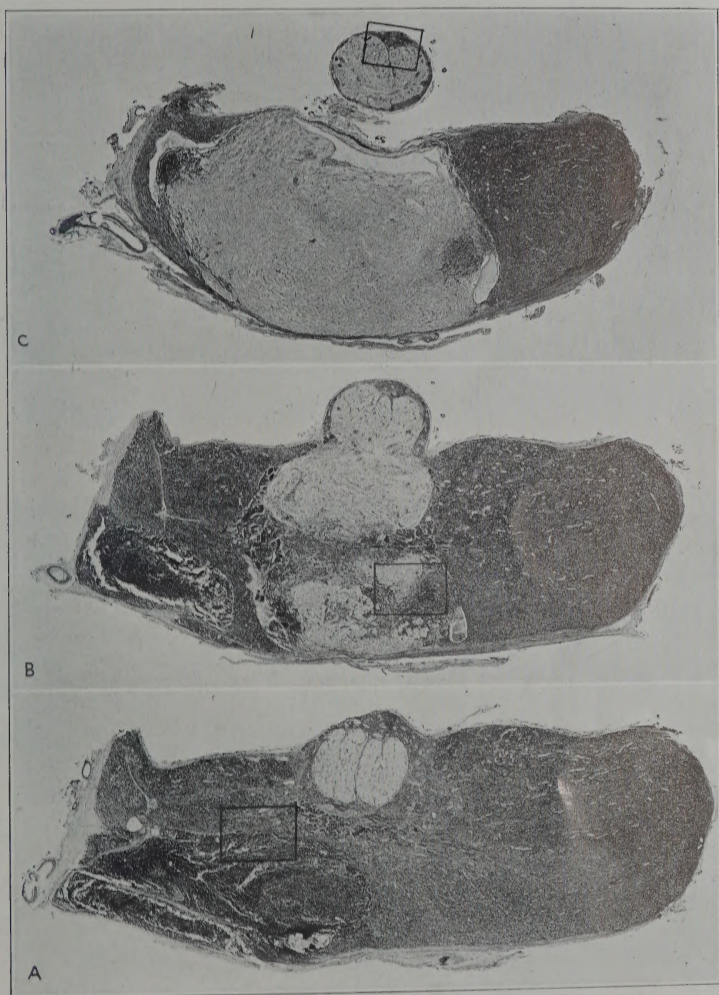


Fig. 23.—Three of the serial coronal sections (magnification $\times 7$) showing: at *A*, greatest measured extent of the adenoma and the anterior margin of posterior lobe surrounded by pars tuberalis; at *B*, extensive basophilic invasion of posterior lobe from pars intermedia; at *C*, transsection of stalk as well as of posterior lobe, small areas of basophilic invasion being still evident at its lateral aspects.

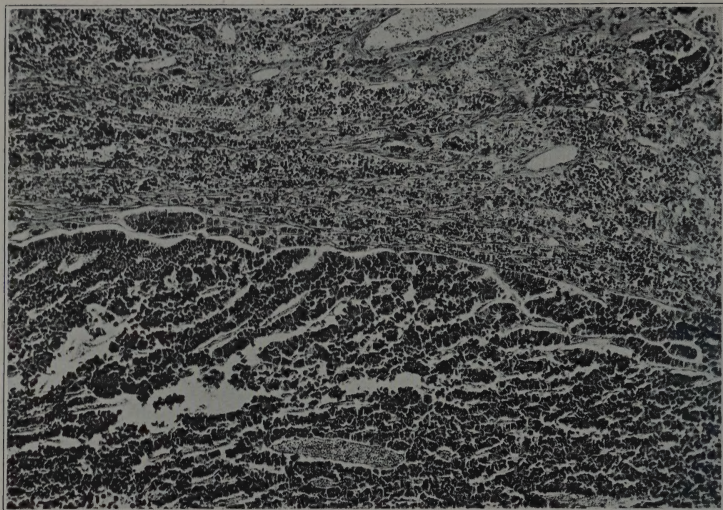


Fig. 24.—Margin of basophilic adenoma (magnification $\times 70$) from squared area in figure 23 *A*. Note small isolated collection of basophils in upper right corner, such as occur in other parts of the lobe.

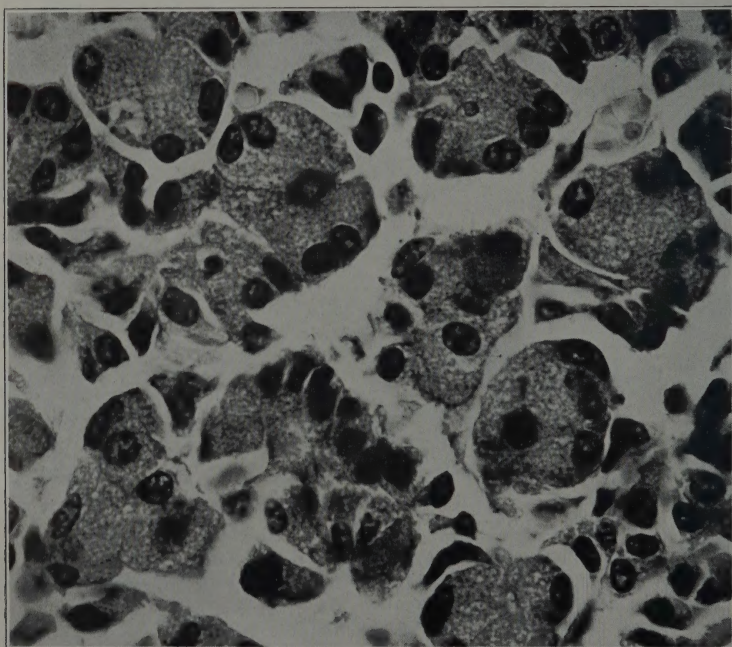


Fig. 25.—Large basophilic elements composing tumor with typical vacuolated cytoplasm (magnification $\times 850$).

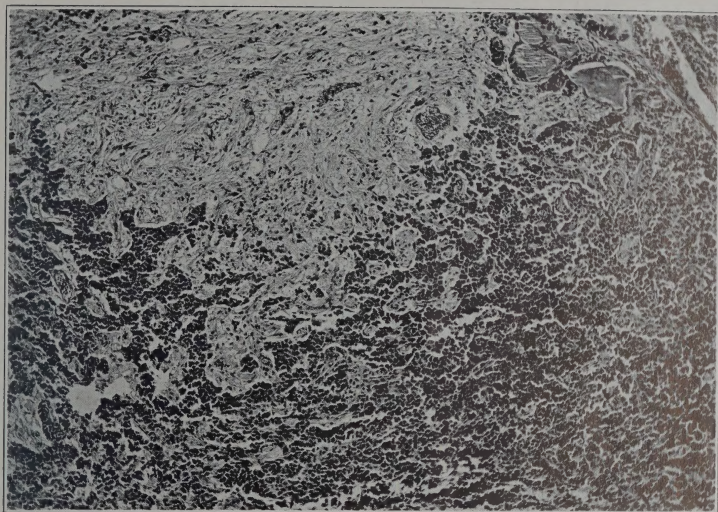


Fig. 26.—Squared area in figure 23 *B* (magnification $\times 70$) showing invasion of the posterior lobe by cords of basophil cells from pars intermedia.

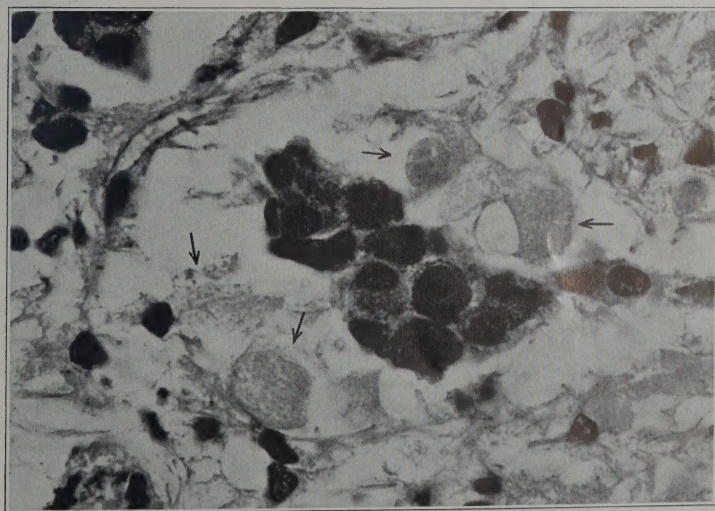


Fig. 27.—Disorgergement of ripened cytoplasm (arrows) of invading basophilic elements into loose tissue spaces of posterior lobe (apocrine secretion), the ghosts of nuclei still apparent in many of the granular masses.

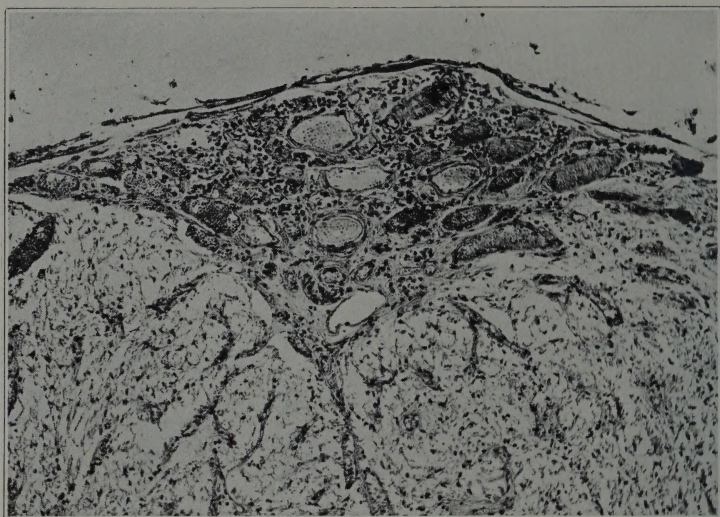


Fig. 28.—Posterior edge of pituitary stalk (cf. squared area in figure 23 C), the bundle of dilated "portal" veins passing from pars distalis through pars tuberalis to hypothalamic (chiefly tuberal) nuclei (magnification $\times 100$).

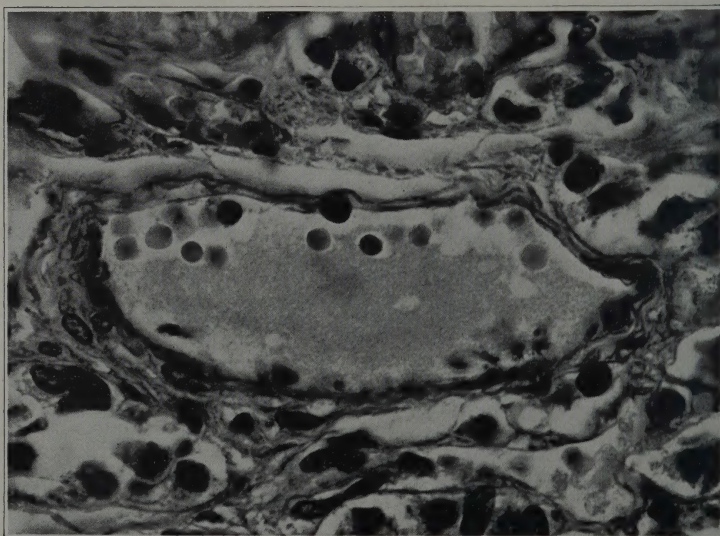


Fig. 29.—A "portal" vein in pituitary stalk so packed with the finely granular secretory product (?) as almost to exclude red blood corpuscles (magnification $\times 850$).

How can one account for the symptomatic effect of this peculiar lesion? That it is an adenoma composed purely of basophilic elements is beyond question. But does it operate merely by pouring its specific hormone into the general circulation, or does the excess of basophilic elements that congregate around the pars intermedia and infiltrate the infundibular lobe indicate the participation of the neurohypophysis in the symptom complex? And if so, does the character of the posterior lobe secretion become modified under these circumstances or merely increased?

The attempt to answer these questions obliges us to consider: (1) the secondary effects of the "basophilic" hormone, whatever it may be, on the other organs of internal secretion; and (2) the possibility that the posterior lobe has been activated by the lesion. To this possibility we may first turn.

1. BASOPHILIC ACTIVATION OF THE NEUROHYPOPHYSIS

A more or less profuse infiltration of the posterior lobe by viable, normally staining basophilic elements from the pars intermedia has been often described, attention having been first called to it by Thom¹³⁰ (1901) who believed it to be a peculiarity of advancing age. It was noted by Erdheim⁴⁷ (1903) also as a characteristic of old persons; by Löwenstein⁸⁵ (1907) as a feature of the pituitary adenomas; by Herring⁶⁷ (1908) who found that thyroidectomy increased the cellular invasion; by Lucien⁸⁶ (1909) who distinguished the cells as basophilic elements and believed the invasion to be more pronounced in chronic maladies of the aged. It has also been discussed from various aspects by Tölken¹³² (1912), by Plaut⁹⁶ (1922), and by Lewis and Lee⁸² (1927), by Kraus and Traube⁷⁶ (1928), by Berblinger¹⁹ (1927) and most recently by Zondek¹³⁷ (1933) and by Guizzetti⁶² (1933).

With all this accumulative histologic evidence of the frequency of the process, little has been said of its functional significance or of its relation to an associated clinical syndrome. It was once reported as a distinguishing feature of the gland in an early case of acromegaly.⁴¹ However, in no instance has the process been so striking as in the neurohypophysis of this patient, nor have I ever observed before the masses of hyalinoid secretion in the portal vessels of the stalk which are now known to terminate in a plexus surrounding the tuberal nuclei.*

The basophilic elements, consequently, as suggested by the conditions found in the serially sectioned gland of Miss P., may not only exercise their effects through the blood stream, but their product, possibly modified during its passage through the posterior lobe and stalk, may exercise a local effect, presumably stimulatory, on the diencephalic nuclei in whose neighborhood these veins appear to disgorge their product.

* The few sections I have of the Raab-Kraus tumor (cf. fig. 22, case 10³⁸) show also a heavy invasion of basophils apart from the tumor mass which appears to have arisen in the pars intermedia. Professor Kraus mentions this in his protocol.⁷⁶

There is nothing revolutionary in this idea. Herring's conception⁶⁷ (1908) of an infundibular pathway for the secretion of the pars intermedia was independently advanced by Thaon¹²⁰ (1907), by Livon⁸⁴ (1908), by Cushing and Goetsch⁴¹ (1910), and by Edinger⁴⁴ (1911) and was warmly supported by Remy Collin²⁷ (1928) in his monograph, "La neurocrinie hypophysaire." While these observations were for the most part based on the anatomic study of the tissues, it has recently been shown (1933) by Zondek and Krohn¹³⁸ in a series of striking experiments that the pars intermedia elaborates a pigmentary hormone, intermedin, which by a novel and delicate test can be traced through stalk, tuber, and into the fluid of the third ventricle. How many more of the several posterior lobe principles will be found to be similarly distributed remains to be seen.

To such a neurotropic effect, for want of a better explanation, may be ascribed the adiposity, the hypertension and the late vascular changes, which may now be briefly taken up one by one. While it is possible that the glycosurias that occur in these states of basophilism also belong in this same category, their separate consideration will be postponed to a later section dealing with the pancreatic islets. While much that follows is speculative, and based on the examination of this single case, it will at the same time prove, I hope, to be provocative of further study as new opportunities arise.

The Adiposity.—The rapid onset of an obesity which spares the extremities and is chiefly abdominous, while it was not pronounced in this particular patient, has nevertheless been a striking feature in all but one or two of the reported examples of pituitary basophilism (cf. table of cases). We have learned both from animal experimentation and clinical experience that a moderate degree of adiposity is a feature of pituitary insufficiency; but as Smith has so clearly shown in the rat,¹¹⁵ states of extreme obesity comparable to that under consideration can be experimentally produced only by a tuberal injury.

To a presumed injury of the tuber from pressure against the dorsum sellae, Raab¹⁰⁰ ascribed the rapidly acquired obesity of his patient. While this might be mechanically possible with a large tumor, the explanation could scarcely apply to an unenlarged gland. The effect nevertheless may conceivably be a tuberal one, but for quite a different reason—namely, on the basis of a tuberohypophysial mechanism hyperactivated by secretory products from the pars intermedia. And the fact that many of the patients with pituitary basophilism show varying degrees of polyuria and polydipsia is not unfavorable to this interpretation.

The Hypertension.—Whatever may prove to be the cause of the acute adiposity, the attribution of the hypertension, which characterizes the clinical syndrome in all cases, to an excess of neurohypophysial secretion has much in its favor. Compatible with this view is the fact that patients with chromophobe adenomas, which serve to flatten the posterior lobe out of all recognition, invariably have a subnormal blood pressure. Heretofore, the vascular hypertension of polyglandular dis-

orders has been ascribed to an adrenal source; but the hyperplasia solely affects the cortex of these glands and the neural core of chromaffin cells which elaborate epinephrine remains, so far as can be told, histologically unaltered.

The long recognized pharmacodynamic properties of posterior lobe extracts and their relation to the utilization and elimination of water, fat and carbohydrates have only in recent years begun to be interpreted in terms of clinical experience. Hofbauer,⁶⁹ in 1918, in view of the pressor and antidiuretic effects of the extract together with the known enlargement of the hypophysis during gestation, suggested that the pregnancy toxemias, especially eclampsia, might be due to overaction of the posterior lobe. This view has received experimental support by numerous workers, culminating in the demonstration by Anselmino and his collaborators (references 4, 5 and 70) not only of an antidiuretic substance in the blood of all cases of nephropathy and eclampsia, but of a pressor substance as well when the disorders are accompanied by high blood pressure.* Naturally, the substance was looked on as a product of the posterior lobe, which we may take to mean primarily of the pars intermedia.

For many years certain Continental pathologists have given painstaking attention to the cytologic changes in the adenohypophysis in various diseases. Berblinger¹⁸ was the first to call attention to the increase of the basophilic elements of the gland in advanced renal disease, more particularly noticeable in uremia²⁰; and Kraus and Traube⁸⁰ have amplified this to include hypertension and a confusing variety of other disorders. So far as I can determine, however, neither they nor others⁶⁸ who have confirmed their observations have emphasized the significance of the basophilic invasion and resultant activation of the neurohypophysis.

Cholesteremia and Atherosclerosis.—Coincident with the acute adiposity, most of the patients with basophilic adenomas, in whom the determination has been made, have shown a moderate cholesteremia. This Kraus⁷⁸ looks on as the primary factor, the increase of lipoids in the adrenal cortex being secondary, causing in turn the multiplication of the basophilic cells in the pituitary body. However this may be—and it seems an improbable sequence—there can be little doubt of the damaging effect of the cholesteremia on the blood vessels. A deposition of cholesterol esters in the intima Ashoff looks on⁹ as the starting point of atherosclerosis, while the appearance of calcium in the media is a secondary process which appears to be accelerated by active ergosterol produced by irradiation of body lipoids.

The combination of cholesteremia, therefore, with the increase of blood calcium which accompanies the osteomalacia, would seem to be a combination most favorable to the production of the vascular disease seen in these states of pituitary basophilism, the mild degree of nephritis

* Attention should be drawn to the fact that for their tests Anselmino and Hoffmann utilized the rabbit—a notoriously unreliable experimental animal.

being a secondary effect. And it is quite probable that even should the cholesteremia, as in this particular patient, not have been apparent in the later stages of her disease, the stiffening of the vessels which had taken place would in themselves have served to perpetuate her hypertension. In one or two other examples of the disease, a notable fall of blood pressure has coincided with a temporary subsidence of all other symptoms.

2. SECONDARY ENDOCRINE EFFECTS

Should the basophilic cells prove to be responsible for the gonadotropic hormone, the syndrome produced by an adenoma of these elements is scarcely what one would expect. So far as I am aware, however, the gonadotropic hormone from the pituitary body, like that from other sources, has been employed only for short time sex-maturing observations (cf. the early adolescence of Alice D., p. 516, and of Teel's case ¹²⁶), and no one has set out to learn what might be the systemic effects of its continued administration over long periods. While this will undoubtedly come to be done, let us see what interpretation in terms of the experimental laboratory can be offered in the present state of our knowledge for such effects of the three pituitary adenomas as may conceivably be ascribed to functional disturbances of subsidiary glands.

A primary adenoma of any ductless gland doubtless affects by its excessive secretion the secretory activity of all others, just as does the extirpation or pathologic destruction of any one member of the series. But a hypersecretory adenoma or a destructive process in no other gland produces such grossly evident secondary changes in the series as occur when the disorder primarily affects the pituitary body. On this fact the pathologic and experimental evidence of its dominance chiefly rests. What effect primary lesions of the subsidiary endocrine organs actually have on other members of the series is usually shown most strikingly as a reciprocal response on the part of the adenohipophysis itself, e. g., the increase of elements of certain types after thyroidectomy, adrenalectomy and castration.

Unfortunately, we have only fragmentary data regarding the gross and microscopic changes of each subsidiary organ consequent on the experimental withdrawal or increase of the two principal hypophysial hormones separately, chief attention having been paid to the gonads, the thyroid and the adrenal. The sensitivity of the gonads is well known, but the adrenal cortex and thyroid are scarcely less sensitive, as has been amply shown both in the dog and rat. A prompt shrinkage of these structures follows hypophysial extirpation, and a no less prompt hyperplasia follows the injection of prepared extracts of the growth hormone.

Clinicopathologic experience, so far as it goes, coincides with these observations. A chromophobe adenoma whose effects, as we have seen.

are comparable to a more or less complete hypophysectomy, is followed by atrophy of adrenal cortex, of thyroid and of reproductive apparatus. On the other hand, acromegaly, the clinical expression of experimental overgrowth, is associated with a notable hyperplasia of these organs, as has elsewhere been emphasized.⁴⁰

Before entering on a more detailed discussion of these matters, it may be convenient to have before us a diagram (fig. 30), which indicates (roughly, to be sure, for want of a sufficient number of detailed weights and measurements) what gross changes the acidophilic adenomas of acromegaly, what the basophilic adenomas of the disorder

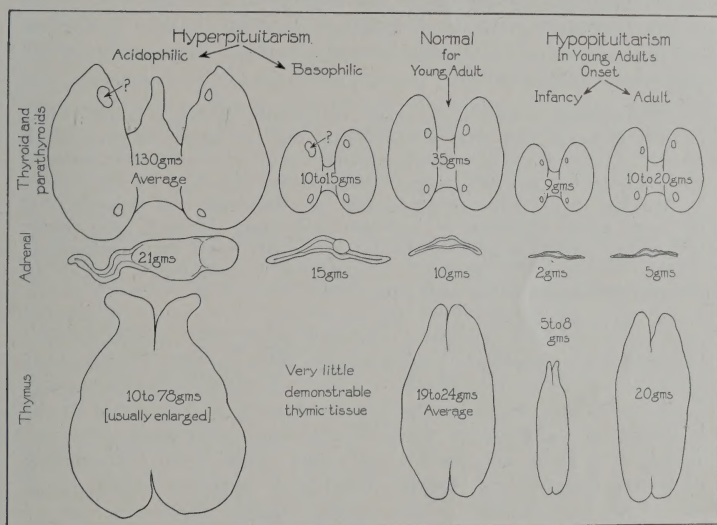


Fig. 30.—A rough diagram (capable of improvement with further data) to indicate, for comparison with the normal organs of the young adult, the secondary changes in the ductless gland series consequent on hyperpituitarism, both acidophilic and basophilic; and on hypopituitarism of young adults which has started (1) in infancy and (2) in adult life. (Reduced two-thirds from natural size.)

under consideration, and what the dual hypopituitarism of chromophobe adenomas tend to bring about. Not enough is known of the interstitial cells of the gonads to represent them in the schema, nor are sufficiently definite changes observable in the pancreatic islets to justify their inclusion.

Symptoms Referable to the Thyroid.—In these states of pituitary basophilism, the thyroid appears to be surprisingly inactive. In the case

under discussion, the gland was small and the basal metabolic rate low on the several occasions when it was tested.* This corresponds to the condition of the gland in hypopituitary states, whether clinical or experimental.

In clinical acromegaly, on the other hand, the gland becomes progressively, sometimes enormously enlarged, and many acromegalics show an elevated metabolism. This may at times be so high that the enlarged thyroid has often been operated on for assumed primary hyperthyroidism. And while this activation of the thyroid with accompanying increase of metabolic rate is usually interpreted in terms of the adeno-hypophysis, it must not be overlooked that posterior lobe extract and its derivatives, pitressin and pitocin, have been shown by Geiling and his co-workers^{58, 61} to have, both in man and dogs, a marked effect on gaseous metabolism.

To experimental alterations of pituitary function, the thyroid, as is well known, responds promptly. Its rapid disorganization and subsequent atrophy, though wrongly interpreted, was observed in our early canine experiments. On the other hand, in experimental gigantism in the rat and dog, the gland becomes quickly hypertrophic. It is now claimed, indeed, by Junkmann and Schoeller^{73, 74} that the gland elaborates a separable thyrotropic hormone, and Evans believes that convincing proof of this lies in the fact that a thyroid-stimulating property remains in the extractives after removal by precipitation of both the growth-promoting and the sex-maturing fractions.

Parathyroid Participation.—The clinical evidences of skeletal decalcification were less marked in the case of Miss P. than in many other recorded examples of the disorder. There was a history of two or three fractures without severe trauma; the roentgenologic appearance of the bones during life betrayed the mild degree of osteomalacia that was found after death, and the multiple renal calculi were characteristic of hyperparathyroidism. On the other hand, she never became round shouldered from collapse of the vertebral bodies, and no increase of calcium elimination was demonstrable at the stage of the disease when her mineral metabolism was under investigation. The glandules were found to be grossly enlarged, but this proved to be due to an interlobular infiltration with fat.

Far more is known about the internal secretion of the parathyroids and its effects than of the cells which produce it. Parathormone, in the opinion of Collip's co-workers,¹³¹ activates the osteoclasts with consequent loss from the skeleton of its calcium phosphate, the kidneys in time becoming affected in their efforts to unload from the blood its excess of mineral salts. In hyperparathyroidism associated with adenomas of the glandules, a wholly similar process occurs, a high blood

* The reading (cf. table of cases) was said to be high in cases 3, 4, 8 and 9, but this in no instance was shown to be associated with any demonstrable hyperplasia in the thyroid when it came to be examined post mortem.

calcium with a low blood phosphorus and increase of phosphatase having been shown by J. C. Aub and his co-workers^{2, 15} to be a uniformly characteristic feature of the malady. But whether in the absence of an adenoma a physiologic activation of the glandules may cause corresponding though milder effects remains conjectural for want of precise information (such as we have for the thyroid gland) regarding the histologic changes in the glandules which are an expression of functional hyperplasia.

Since no definite inter-relationship with other glands of internal secretion has heretofore been established for the parathyroids, it is venturesome on symptomatic grounds alone to suggest that we have clinical evidence of it here. With one possible exception, no abnormalities of any kind have been observed in the parathyroid bodies of persons who have succumbed to pituitary basophilism. The exception was a case reported twenty years ago, first briefly by Schmorl,¹¹¹ and subsequently more in detail by Molineus⁸⁹ together with two other examples of advanced osteitis deformans, in both of which a parathyroid adenoma was found. Naturally enough, therefore, the osteomalacia in the third case was likewise ascribed to hyperparathyroidism on the basis of an oxyphilic hyperplasia without adenomatous formation. Clinically, this case, as reported, had all the hallmarks of the malady under discussion. The large basophilic adenoma which was found post mortem was looked on as an incidental lesion playing no part in the syndrome.

Osteomalacia, indeed, has often been so striking a feature of the post-mortem findings in pituitary basophilism that the protocol of the autopsy has been largely given over to it. Nevertheless, it is rare for the process to be so marked that it could be mistaken for von Recklinghausen's generalized osteitis fibrosa. It may be that this advanced type of decalcification may require an amount of parathormone quite beyond the capacity of a simple hyperplasia and only be delivered by a functionally active parathyroid adenoma.

Unfortunately, the parathyroid glandules have not always been looked for and examined, but when this has been done an unmistakable adenoma has never been detected. And apart from the multiple skeletal lesions in the Molineus case, the only instance of a possible "brown tumor" occurring in a patient with pituitary basophilism was the pelvic lesion roentgenologically picked up in the case of Alice D., to which brief allusion has just been made (p. 516).

The Thymus.—A thorough dissection of the mass of mediastinal fat in this patient failed to detect any isolated organ, and only shreds suggestive of thymic tissue were microscopically demonstrable. Similarly, in all other cases of basophilism that came to autopsy the gland has been reported as small whenever specific reference has been made to it. To this, however, there is one notable exception, namely, the case

with many of the clinical features of pituitary basophilism reported by Leyton, Turnbull and Bratton⁸³ in which a cancer of the thymus was found in the absence of any pituitary abnormality.

On the other hand, the thymus may be greatly enlarged in association, curiously enough, both with chromophobe and with acidophilic adenomas. In what was probably the first case of acromegaly ever thoroughly examined post mortem, Fritsche and Klebs⁵⁵ found the thymus to be so markedly hypertrophic they were inclined to ascribe the disease to this source rather than to the less strikingly large pituitary body. Just what these hyperplastic revivals of the dormant structure signify, the Sphinx among the glands of internal secretions (if it actually is one of them) has not yet revealed.*

Pancreatic Islets versus Hypophysis in Sugar Metabolism.—The patient, as will be recalled, came under Dr. Joslin's care because of her glycosuria, a symptom which has been even more marked in other examples of the disorder. In one instance (case 11 of an earlier report³⁸) during an acute exacerbation of the malady the hyperglycemia was found to be uncontrollable by insulin. Since then, however, the glycosuria of that patient has spontaneously subsided; and as the adiposity and hypertension have also grown less, he, at the present time, in spite of the residual stigmas of the disease, enjoys reasonably good health.

Similar waves of hyperglycemia, as is well known, characterize acromegaly. In this disorder also, not only is the glycosuria difficult to control by insulin, but it may sometimes spontaneously disappear when hypopituitary symptoms ultimately come to be superimposed on the original clinical picture. In view of all this, doubts naturally arise regarding the rôle of the pancreatic islets in pituitary (acidophilic or basophilic) diabetes, for what is known as primary pancreatic diabetes shows no remissions of this sort.

Allusion has already been made (p. 489) to the peculiar state called cachexia hypophyseopriva which we observed as a sequel of our early canine hypophysectomies and which usually proved fatal. While we did not then know enough about carbohydrate metabolism to realize that this might represent a state of acute sugar deprivation (now known as hypoglycemic shock), we did soon learn that a greatly increased tolerance for carbohydrates would be shown by the animals that recovered from the operation. And we soon learned, too, that a corresponding high tolerance for sugars was characteristic of clinical hypopituitarism. It was already known that posterior lobe extracts caused glycosuria in certain animals, and we were therefore misled into ascribing the disturbances of sugar metabolism solely

*What may be the relation, if any, of the fat organ of batrachians and of hibernating mammals to the thymus I am not enough of a comparative zoologist to know. It will be recalled that in the Smiths' early report¹¹⁹ on the responses of the tadpole to hypophysectomy, the thyroid, parathyroid and adrenals failed to develop, but the fat organ remained hypertrophic; injections of posterior lobe extract caused it to disappear (cf. Rasmussen¹⁰²).

to this part of the gland.* Hence, after working over the problem at length, it was stated⁶⁰ that: "If loss or diminution of the internal secretion of the pancreas robs the tissues of their power of metabolizing carbohydrates, certainly loss or diminution of the hypophyseal posterior lobe greatly enhances their power in this respect." So marked was the degree of tolerance for sugar, we had come to believe that a preliminary hypophysectomy might actually counteract the fatal effects of removing the pancreas, but we never got so far as to put this to the supreme test of a total pancreatectomy.

It meanwhile had been observed by Aschner⁸ that after a transphenoidal hypophysectomy glycosuria could be easily produced by a piqure of the tuber. And this was also found to be true in the course of our later efforts¹³⁴ to work out the autonomic control of the gland by tracing the pathway of neuroglycosuric discharges. That the tuberal nuclei directly controlled the neurohypophysis was then not even surmised.

New light was thrown on the question favorable to posterior lobe participation in carbohydrate metabolism, when Burn²⁶ (1923) discovered the antagonistic effect of insulin and neurohypophyseal extracts, the latter serving to counteract the symptoms of hypoglycemia. Others promptly corroborated this observation, and it was soon found by Houssay and Magenta⁷² (1924) that hypophysectomized dogs are hypersensitive to injections of insulin; and the same now proves to be true of hypophysectomized monkeys⁶⁴ and also of patients with a marked hypopituitary syndrome.

This was further amplified in an important paper (1927) by Geiling and others,⁵⁷ who showed not only that removal of the canine anterior lobe alone, leaving the posterior lobe intact, failed to cause insulin hypersensitization, but also that the hypoglycemic "shock" so easily produced by giving insulin to totally hypophysectomized dogs can be prevented by the coincidental injection of posterior lobe extract. Finally, Cowley³⁰ has recently (1931) demonstrated the presence in the blood of hypophysectomized dogs of a substance having a marked hypoglycemic action. All things considered, therefore, evidence abounds that the high tolerance for carbohydrates in hypopituitary states is due to an increase of the insulin content of the blood due to the withdrawal of the counteractive posterior lobe principle.

So much, then, in behalf of the neurohypophysis. What now can be said of the adenohypophysis in relation to sugar metabolism?

While it was observed that some of our laboratory dogs, in process of becoming acromegalized by injection of Evans' growth hormone, showed hyperglycemia, the problems this suggested were not pursued. They, however, have been seriously attacked in a telling series of experiments conducted during the past three years by

* In recent years it has been shown by Geiling and Eddy⁵⁹ that posterior lobe extract and its derived products, pitressin and pitocin, produce hyperglycemia; also by Nitzescu and Benetato⁹¹ that there is a coincidental increase of inorganic phosphate in the blood.

Houssay and Biasotti⁷¹ who have shown that diabetes fails to develop in hypophysectomized toads on subsequent removal of the pancreas. When, however, toads in this precarious state of experimental carbohydrate balance are given subcutaneous implantations of the anterior lobe of fishes, birds or mammals, they immediately become diabetic. Though this effect is less striking in hypophysectomized dogs subsequently deprived of the pancreas, they acquire a diabetes of slow evolution with long periods of remission in which hypoglycemic crises may occur. It has also been shown by the Argentine physiologists that administration of the growth hormone to normal rats and dogs will provoke glycosuria with polyuria and hyperglycemia, and they go so far as to predict the discovery of a pituitary diabetogenic hormone which plays the predominant if not exclusive rôle in carbohydrate metabolism.

There is only one way of reconciling these contradictory views regarding posterior vs. anterior lobe control over the utilization of sugar—and that is to accept them both as correct with another interpretation. This interpretation is that which has already been advanced as an explanation of the hypertension: namely, that the pars intermedia cells pass into and activate the neurohypophysis.*

But whatever may prove in the end to be the correct explanation, there is evidence at hand that extracts of both anterior and posterior lobe exercise an antagonistic effect on insulin. Whether this effect is produced by inhibition of the islets or by extrapancreatic neutralization of liberated insulin remains undetermined. From an histopathologic standpoint, while primary pancreatic diabetes is said to be accompanied in something over half of the cases by demonstrable lesions of the islet tissue, no corresponding changes have ever been convincingly described either in acromegaly with hyperglycemia or in the few instances of pituitary basophilism in which autopsy was performed.

All said and done, there is possibly no more reason why we should expect to find the islets appreciably atrophic in these maladies than to find them hyperplastic in the counter-states of pituitary deficiency in which the tolerance for carbohydrates is increased. Histopathology has its limitations, and the function of cells may conceivably be altered without recognizable change of form.

The Adrenal Participation in the Syndrome.—Hypertrophy of the adrenal cortex was one of the striking features of Miss P.'s case, as it has been of most other instances of basophilism that have had a post-mortem verification. It is chiefly shown in the zona fasciculata whose cells are distended by an increase in their lipoid content. Certain

* The reciprocal effects on the hypophysis of disordered function of the pancreatic islets has received scant attention from the anatomic side. Kraus⁷⁵ described a shrinkage of the gland particularly noticeable in the pars intermedia after pancreatectomy in the cat—an observation which others failed to substantiate. Eaves,⁴³ on the other hand, briefly reported that prolonged injection of small doses of insulin in rabbits causes enlargement of the hypophysis and changes suggesting cellular hyperplasia, both of the pars intermedia and the pars anterior.

features of the syndrome so strongly suggest a primary hyperadrenalism it is not surprising that several of the patients in the series should have been subjected to a suprarenal exploration with unilateral adrenalectomy. And the fact that a definite though small adenoma of cortical elements has been found in one or two instances has been highly misleading.*

The basophilic elements, therefore, whatever the nature of their hormone, evidently elaborate a substance which has a highly stimulating

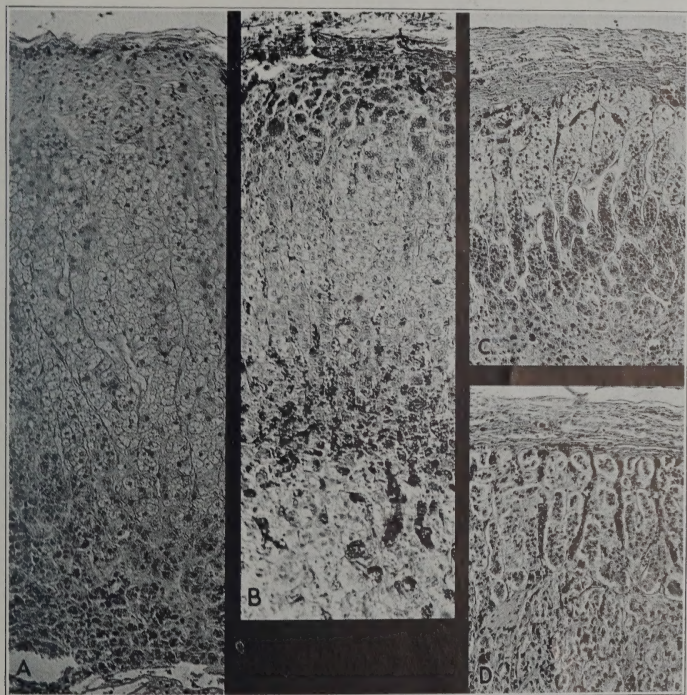


Fig. 31.—Adrenal cortex (magnification $\times 80$) from: *A*, the case of pituitary basophilism; *B*, an acromegalic; *C*, an adult with hypopituitarism from chromophobe adenoma; *D*, an adult pituitary dwarf, aged 27.

effect on the adrenal cortex. The accompanying photograph (fig. 31) indeed suggests that the degree of hyperplasia exceeds even that produced by the acidophilic elements in acromegaly. To put to a compara-

* That an accessory para-ovarian nodule of adrenal tissue was found in this and another case of basophilism need cause no surprise in view of the embryogenic relation of both adrenal gland and reproductive apparatus to the wolffian body.

tive test the effect on the cortex of the growth principle and of a sex-maturing principle the following study (unpublished) was made a year ago at my request by Drs. Thompson and Troppoli:

For the experiment were used three groups of three immature litter-mate female rats. All nine animals were 45 days old and, with trifling variations, weighed 60 Gm. apiece. Of each group of three, one member was used as a control; a second member was given twice daily a parenteral injection of 0.5 cc. of a modified anterior lobe preparation; the third member was given twice daily 0.5 cc. of prolant-containing urine of pregnancy (the adenohipophysial gonadotropic substance would have been preferred but none was at hand).

The introitus of all three animals receiving prolant opened on the fourth day, whereas this took place in the case of the three controls and of the three animals receiving growth hormone at variable times, averaging about seventeen days.

Throughout the experiment, all animals were given an ordinary diet and were killed at the expiration of seventy-two days, during which time the three control animals had gained ca. 85 Gm., those injected with growth extract ca. 120 Gm., and those injected with prolant, an average of only 70 Gm. (one of them lost weight from a slight infection).

On the fifteenth day of the experiment, the right adrenal and ovary were removed from each of the first trio, the weights of the cleanly stripped adrenals being as follows: control, 9 mg.; growth hormone, 10 mg.; prolant, 112 mg.

On the forty-seventh day, the adrenals were removed from the second trio and gave the following weights: control, 16 mg.; growth hormone, 22 mg.; prolant, 20.5 mg.

On the fifty-second day, the adrenals removed from the third trio gave these weights: control, 20 mg.; growth hormone, 16 mg.; prolant, 27 mg.

When all nine were killed on the seventy-second day of the experiment, the animals being 117 days old, the remaining adrenal of each of the first trio weighed: control, 26 mg.; growth hormone, 24 mg.; prolant, 37 mg. The adrenals of the second trio weighed: control, 36 mg.; growth hormone, 45 mg.; prolant, 51 mg. The adrenals of the third trio weighed: control, 20 mg.; growth hormone, 14 mg. (this animal had a terminal infection); prolant, 47 mg.

While it is known that the female rat not only has heavier pituitary glands but also heavier adrenals than the male, a disproportion which increases with age, an estimate of the weight of the normal adrenal at ca. one hundred and seventeen days is given as 20 mg. (Donaldson). Needless to say, the enlargement of the organs above this weight was due solely to a cortical hyperplasia.

From this experiment, which as we shall see runs counter to the experience of others, it was deduced that among the known sexmaturing substances, prolant at least serves as an adrenocortical stimulant.

A secondary adrenal hyperplasia was shown by Evans to be one of the striking features of experimental gigantism in the rat, while an actual cortical adenomatosis was described by Putnam and his associates⁹⁹ in their first example of canine acromegaly; and though we cannot be quite sure to which of the two principal hormones this change was attributable, in view of the unpurified extract that was used in these experiments, it was probably due to that of growth.

What may be the condition of the adrenals in hereditarily dwarfed mice, in which the growth factor alone is deficient, I do not know; but

when there is dual hypopituitarism (cf. fig. 32), whether produced by a chromophobe adenoma or by an experimental hypophysectomy affecting both elements, cortical atrophy may be extreme. It was shown by Smith¹¹⁵ that the weights of the adrenals of hypophysectomized rats will shrink within six days to one-half the size of the controls. What is more, the atrophic glands of these animals can be promptly restored to normal or near normal by glandular implantations, which, of course, contain both growth and sex fractions.

Evans, however, finds (personal communication) that purified growth hormone by itself will restore almost to normal the atrophic adrenals of hypophysectomized rats if treatment is instituted soon after the hypophysectomy. At the same time, he is convinced that the gonadotropic substance in pregnant-mare serum and that in the urine of pregnant women have no effect whatever on the adrenal cortex (the influence of the pituitary sex principle itself was not investigated), which controverts the Thompson-Troppoli experiments just cited.

The adrenal cortex is known to be essential to life, a bilateral adrenalectomy leading to symptoms which, even to the extreme fall in

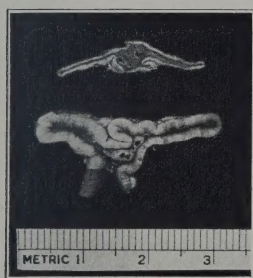


Fig. 32.—To compare (natural size) the atrophic adrenal cortex of adult hypopituitarism (above) produced by a chromophobe adenoma with the hyperplasia of pituitary basophilism (below) shown in this case; both persons approximately same age.

body temperature and marked loss of weight, closely resemble the acute cachexia hypophyseopriva often observed after hypophysectomy in adult dogs. Beyond this, and the fact that these symptoms may be overcome and an essentially normal condition reestablished by the injection of a cortical extract, those who have worked most extensively in the field of adrenal physiology confess¹²² to scant knowledge of what the normal function of the cortical hormone may be.¹²³

Of the relation of the cortex to the enclosed neuromedullary part of the gland which secretes epinephrine, we know even less than we do of the relation of the adenohypophysis to the neurohypophysis which it envelops. This admission is the more remarkable in view of the peculiar and striking syndromes which are clinically

known to accompany what presumably are primary, often malignant, adenomas of the adrenal cortex and of the chromaffin tissue of the medullary substance. Characteristic features of these syndromes are hypertension, hypertrichosis, deviations of secondary sex qualities such as the masculinization of women, and even glycosuria.

While nothing is known of the reciprocal pituitary changes accompanying these clinical states of primary hyperadrenalism, an increase of basophilic elements might be anticipated if, as stated by Kraus⁷⁷ and by Berblinger,²¹ these elements are notably diminished in number in cases

of Addison's disease. However this may be, when a syndrome akin to that of hyperadrenalism occurs in association with a definite basophilic adenoma, as in the case under discussion, the hypertrophic changes in the adrenal cortex, to which the symptoms are naturally ascribed, can scarcely be interpreted as other than a secondary effect.

Gonadal Effects.—We have seen that in this patient there was an early period of amenorrhea followed by a long interval of fairly normal menstruation, when again a two year period of menstrual cessation occurred and preceded death. The disorder therefore showed periods of symptomatic exacerbation and remission, just as hyperthyroidism or acromegaly may occur in successive waves of activity.

The ovaries, as recorded in the protocol, while essentially normal in appearance (fig. 33), gave evidence of follicular stimulation in the absence of luteinization resembling in this respect the ovaries of acromegaly⁴⁰ and of adult rats treated with pituitary transplants.¹¹⁶ The changes in the theca interna (fig. 34), consisting of increased vascularization with an epithelioid transformation and vacuolization of the cells, are those known to occur (Corner²⁹) during the period preceding maturation of the ovum.* They are looked on by many as the true interstitial cells of the ovary† and while they may possibly participate in the formation of the corpus luteum, evidence seems to favor the granulosa cells as the chief source of this body. Theca cells heavily laden with lipoids appear in the corpus albicans only after granulosa cells have disappeared.

It is claimed⁵⁴ that the adeno-hypophysial gonad-influencing principle can be divided into two separable fractions, one having follicularizing and the other luteinizing properties. From the condition of the ovaries of this patient it would appear that the follicularizing stimulus is present but that the element to complete the ovulatory cycle with rupture and luteinization of the follicle is absent, thus accounting for

* Since this paragraph was written, Dr. G. W. Corner, having kindly examined the sections, states it to be his belief that the normal processes of follicular growth have been in abeyance for some time and that the ovary resembles that of a patient in the early menopausal years. While the primordial ova are in good condition, there is a striking absence of medium-sized follicles and the granular cells of all the large follicles are in the early stage of atresia, showing breakdown of the nuclei. His assumption would be, therefore, that the ovary for some reason was not receiving its normal stimulus to cyclic growth.

† The possible relation of the interstitial cells of ovary and testis to the secondary characters of sex is a complicated and disputed subject¹⁰³ which cannot here be gone into, though the bearded faces of women with pituitary basophilism suggest that something in this direction is abnormal. Collip has recently shown²⁸ that when the "anterior pituitary-like hormone" of the placenta is administered to hypophysectomized male rats, the usual atrophic changes in the reproductive apparatus are limited to a degeneration of the germinal epithelium, whereas the interstitial cells are increased and the accessory sex organs fail to undergo atrophy.

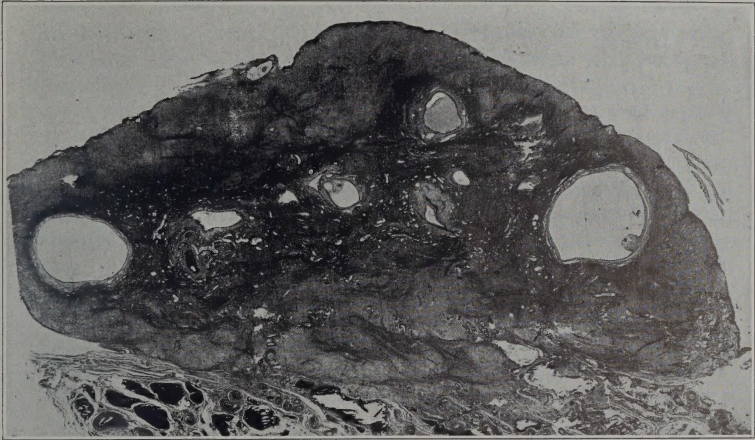


Fig. 33.—Section of patient's ovary (magnification $\times 5$) to show surface appearance, situation and number of cysts and of corpora atretica.

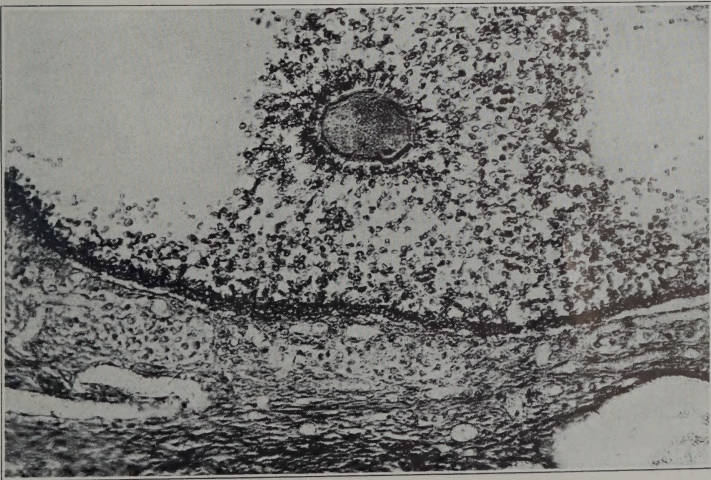


Fig. 34.—Degenerated oocyte in cumulus and active theca interna (magnification $\times 150$).

the amenorrhea. Her urine was tested on immature female rats for gonad-stimulating properties with negative effects and the same was true of another patient (case 11 of another report³⁸) in the series. On the other hand, the urine of the young girl whose photographs have been shown (cf. fig. 14) proves to have a follicularizing effect on young rabbits, so that some more sensitive recipient than the rat—the ring dove, for example¹⁰⁸—may be necessary for the detection of these substances.*

The patient's small uterus with its thin atrophic endometrium was the opposite of that seen in acromegaly, both clinical¹²⁵ and experimental,⁹⁹ an enormous hyperplasia of vagina, uterus, tubes and endometrium being characteristic of these states.

As already pointed out, the evidence to show that the basophilic cells are concerned with the gonadotropic hormone is contradictory and inconclusive. Just what would be the somatic effect of prolonged administration of the adenohipophysial sex principle by itself is unknown and for the same reason it is unknown what changes would be produced in the ovary and reproductive tract by such long continued stimulus. Excessive luteinization of the ovary was shown by Evans and Long⁵⁰ (1921) to follow the prolonged administration of their original growth extract. But since the preparation then employed was not free of the gonadotropic principle, this was a complicating factor in the early experimentally produced states of gigantism both in rats and dogs and largely explains the associated gonadal effects that were observed.

Even though from the adenohipophysis of the sheep an active sex hormone may be prepared, it proves not to stimulate the ovulatory mechanism in the same way in all species, so that experimental data will scarcely be transferable to man until animals higher in the series⁶⁴ (possibly in the end, anthropoids) are employed. The whole subject has become further complicated and attention has been distracted from the pituitary hormone to the study of similar substances more easily obtained. This was brought about by Aschheim and Zondek's discovery⁶ of a sex-maturing product (prolan) in the urine of pregnant women, numerous substances with similar properties having since been found in other body fluids or tissues in varying concentrations in different animals. Whether these several substances are the same as the pituitary hormone, as some take for granted, or merely serve as activators of it,⁵¹ or represent products derived from it, or have nothing to do with it other than that their biologic effect on maturation is similar will not be known until the precise chemical formula of each comes to be worked out.

* In appraising these reactions, it should not be overlooked that those competent to pass on the question of separate follicle-stimulating and luteinizing hormones do not feel that there is adequate evidence of their separate existence.

Meanwhile, in view of their variable source of origin and variable action on different species, they have, if anything, served temporarily to confuse rather than to simplify our understanding of the direct pituitary influence on the peculiar chain of events concerned with the ripening, discharge, insemination and implantation of the ovum. It is a delicate mechanism easily disturbed. And while the condition of the ovary might be expected to give evidence of the nature of the product elaborated by a basophilic adenoma, in the present state of our knowledge its pathologic and symptomatic effects are difficult to appraise.

While fully believing that the adenohypophysis is the root of all this evil relating to disturbances of growth and sexual activity, it seems almost too much specifically to charge it with thyroid-activating, glyco-genic, lactogenic, metabolizing, follicle-stimulatory, pigment-affecting, luteinizing and menstrual-initiating properties and other petty crimes of like sort for which its subordinate accomplices may well enough be responsible.

CONCLUSIONS

During the past two decades, much has been learned about pituitary dysfunction from many angles: from comparative and experimental zoology most of all; from clinical pathology a great deal; something from histologic cytology; and as yet, all too little from biochemistry to which we pin our chief hope.

Whereas the pituitary body was once looked on as a functioning whole, this idea was disrupted when Howell showed in 1898 that its blood pressure-raising effect was confined to extracts of the posterior lobe. Since then, an ever mounting number of properties suggesting separate chemical messengers have come to be ascribed to one or another subdivision of the gland—those of the posterior lobe giving acute pharmacodynamic responses, those of the anterior lobe producing their effects more slowly.

After Howell's discovery, fifteen years passed before it was found that posterior lobe extracts could control diabetes insipidus, and ten years more before the relation of this disorder to certain clusters of nerve cells in the hypothalamus was appreciated. And now after a lapse of thirty-five years, the fact that posterior lobe overactivity may be responsible for a number of hitherto obscure clinical disorders has only begun to be realized.

Attention meanwhile has been chiefly focused on the properties of anterior lobe extracts whose remarkable effects have served further to emphasize the dominance of the gland over other members of the endocrine series. Much, indeed, that has already been done in studying these subsidiary glands as isolated and independent structures needs redoing and reinterpreting. And at the same time the conception that anterior lobe, posterior lobe and interbrain work in harmony and cannot well be studied separately has been clearly demonstrated.

The pituitary adenomas have been made the subject of this lecture with the intent of drawing renewed attention to these processes as secretory "stills" which, in spite of their pathologic structure, nevertheless in all probability are elaborating an excess of the normal hormones. Not until we have learned how to incite in experimental animals an actively and continuously secreting lesion of this sort can we expect precisely to reproduce, and thereby fully to interpret the effects of Nature's prolonged experiment on man.

In order to gage what substance if any is secreted by the different adenomas, the patient's blood and urine as well as tissue from the tumor itself when available will some day have to be tested for the presence of each of the accepted as well as of the several predicated hormones of the normal gland. But only when these tests come to be more simplified than they now are will it be possible definitely to say: whether a chromophobe adenoma, like that of the dwarfed child, actually has any secretory product; whether the overgrowth in lads like those described is due to an excess of the growth principle; whether or not the blood of the acromegalic woman was flooded with a separable lactogenic hormone; and what may have been the nature of the substance elaborated by the tumor in the case of the unfortunate young woman so long victimized by pituitary basophilism.

But however much of all that I have said regarding these adenomas and their secretory effects may be fact and how much fancy, we may be sure that in the course of time the greater part of it will be modified out of all recognition. Consequently, should this second lecture on dyspituitarism prove twenty years hence to have contained a modicum of truth, so helpful to our further understanding of pituitary function in disease as was the attribution of adiposogenital dystrophy and retardation of growth to pituitary insufficiency, that would be recompense enough for me and sufficient justification, I hope, for the act of the Harvey Society.

BIBLIOGRAPHY

1. Addison, W. H. F.: The Cell-Changes in the Hypophysis of the Albino Rat After Castration, *J. Comp. Neurol.* **28**:441-461, 1917.
2. Albright, F.; Bauer, W.; Ropes, M., and Aub, J. C.: Studies of Calcium and Phosphorus Metabolism: IV. The Effect of the Parathyroid Hormone, *J. Clin. Investigation* **7**:139-181, 1929.
3. Anderson, J.: A Case of Polyglandular Syndrome with Adrenal Hypernephroma and Adenoma of the Pituitary Gland, *Glasgow M. J.* **83**:178-192, 1915.
4. Anselmino, K. J., and Hoffmann, F.: Nachweis der antidiuretischen Komponente des Hypophysenhinterlappenhormons und einer blutdrucksteigernden Substanz im Blute bei Nephropathie und Eklampsie der Schwangeren, *Klin. Wchnschr.* **31**:1438-1441, 1931.
5. —Hoffmann, F., and Kennedy, W. P.: The Relation of Hyperfunction of the Posterior Lobe of the Hypophysis to Eclampsia and Nephropathy of Pregnancy, *Edinburgh M. J.* **39**:376-388, 1932.

6. Aschheim, S., and Zondek, B.: Die Schwangerschaftsdiagnose aus dem Harn durch Nachweis des Hypophysenvorderlappenhormons, *Klin. Wchnschr.* **7**:1404-1410, 1928.

7. Aschner, B.: Ueber die Folgeerscheinungen nach Exstirpation der Hypophyse, *Verhandl. d. deutsch. Gesellsch. f. Chir.* **39**:46-49, 1910.

8.—Ueber die Funktion der Hypophyse, *Arch. f. d. ges. Physiol.* **146**:1-146, 1912.

9. Ashoff, L.: The Relationship Between Cholesterin, Metabolism and Vascular Disease, *Brit. M. J.* **2**:1131-1134, 1932.

10. Babinski, J.: Tumeur du corps pituitaire sans acromégalie et avec arrêt de développement des organes génitaux, *Rev. neurol.* **8**:531-533, 1900.

11. Bailey, P., and Cushing, H.: Studies in Acromegaly: VII. The Microscopical Structure of the Adenomas in Acromegalic Dyspituitarism (Fugitive Acromegaly), *Am. J. Path.* **4**:545-564, 1928.

12.—and Davidoff, L. M.: Concerning the Microscopic Structure of the Hypophysis Cerebri in Acromegaly, *Am. J. Path.* **1**:185-207, 1925.

13. Basir, M. A.: The Vascular Supply of the Pituitary Body in the Dog, *J. Anat.* **66**:387-398, 1932.

14. Bauer, J.: Ueberfunktion des gesamten Nebennierensystems ohne anatomischen Befund, *Wien. klin. Wchnschr.* **43**:582-586, 1930.

15. Bauer, W.; Albright, F., and Aub, J. C.: A Case of Osteitis Fibrosa Cystica (Osteomalacia ?) with Evidence of Hyperactivity of the Parathyroid Bodies, *J. Clin. Investigation* **8**:229-248, 1930.

16. Benda, C.: Ueber den normalen Bau und einige pathologische Veränderungen der menschlichen Hypophysis cerebri, *Arch. f. Anat. u. Physiol. (Physiol. Abt.)*, 1900, 373-380; Die mikroskopischen Befunde bei vier Fällen von Akromegalie, *Deutsche med. Wchnschr.* **27**:537-539, 564-566, 1901.

17. Benedict, E. B.; Putnam, T. J., and Teel, H. M.: Early Changes Produced in Dogs by the Injections of a Sterile Active Extract from the Anterior Lobe of the Hypophysis, *Am. J. M. Sc.* **179**:489-497, 1930.

18. Berblinger, W.: Zur Basophilenvermehrung im menschlichen Hirnanhang, *Centralbl. f. allg. Path. u. path. Anat.* **30**:617-619, 1919-1920.

19.—Kritisches zur Hypophysenpathologie, *Frankfurt. Ztschr. f. Path.* **35**:497-524, 1927.

20.—Die Menge der basophilen Epithelien in der Adenohypophyse des Menschen bei chronischer Glomerulonephritis, entzündlicher Schrumpfniere, bei den Nephrosklerosen und bei Urämie, *Virchows Arch. f. path. Anat.* **275**:230-249, 1929.

21.—Pathologie und pathologische Morphologie der Hypophyse des Menschen, in Hirsch, M.: *Handbuch der inneren Sekretion*, Leipzig, Curt Kabitzsch, 1932, vol. 1, pp. 909-1097.

22.—Die Korrelationen zwischen Hypophyse und Keimdrüsen, *Klin. Wchnschr.* **11**:1329-1333, 1932.

23. Bishop, P. M. F., and Close, M. B.: A Case of Basophil Adenoma of the Anterior Lobe of the Pituitary, *Guy's Hosp. Rep.* **82**:143-153, 1932.

24. Bryan, A. H., and Gaiser, D. W.: The Influence of Diet and the Anterior Growth Hormone on the Growth Rate of Adolescent Rats, *Am. J. Physiol.* **99**:379-390, 1932.

25. Bugbee, E. P.; Simond, A. E., and Grimes, H. M.: Anterior Pituitary Hormones, *Endocrinology* **15**:41-54, 1931.

26. Burn, J.: Modification of the Action of Insulin by Pituitary Extract and Other Substances, *J. Physiol.* **57**:318-329, 1923.
27. Collin, R.: *La neurocrinie hypophysaire*, Paris, Gaston Doin, 1928, 102 pp.
28. Collip, J. B.; Selye, H., and Thomson, D. L.: Gonad-Stimulating Hormones in Hypophysectomised Animals, *Nature (Lond.)* **131**:56, 1933.
29. Corner, G. W.: Cytology of the Ovum, Ovary and Fallopian Tube. Cowdry: *Special Cytology*, New York, Paul B. Hoeber, Inc., 1928, vol. 2, pp. 1111-1150.
30. Cowley, R. J.: Hypoglycemic Action of Hypophysectomized Dog's Blood, *J. Pharmacol. & Exper. Therap.* **43**:287-293, 1931.
31. Crowe, S. J.; Cushing, H., and Homans, J.: Effects of Hypophyseal Transplantation Following Total Hypophysectomy in the Canine, *Quart. J. Exper. Physiol.* **2**:389-400, 1909.
32. ———Experimental Hypophysectomy, *Bull. Johns Hopkins Hosp.* **21**:127-169, 1910.
33. Cushing, H.: Sexual Infantilism with Optic Atrophy in Cases of Tumor Affecting the Hypophysis Cerebri, *J. Nerv. & Ment. Dis.* **33**:704-716, 1906.
34. ———The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism, *J. A. M. A.* **53**:249-255 (July 24) 1909.
35. ———Acromegaly from a Surgical Standpoint, *Brit. M. J.* **2**:1-9; 48-55, 1927.
36. ———The Chiasmal Syndrome of Primary Optic Atrophy and Bitemporal Field Defects in Adults with a Normal Sella Turcica, *Arch. Ophth.* **3**:505-551 (May); 704-735 (June) 1930.
37. ———Papers Relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System, Springfield, Ill., Charles C. Thomas, 1932, 234 pp.
38. ———The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), *Bull. Johns Hopkins Hosp.* **50**:137-195, 1932.
39. ———Further Notes on Pituitary Basophilism, *J. A. M. A.* **99**:281-284 (July 23) 1932.
40. ———and Davidoff, L. M.: The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance, Monograph Rockefeller Institute for Medical Research, no. 22, 1927, 131 pp.
41. ———and Goetsch, E.: Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and Its Presence in the Cerebrospinal Fluid, *Am. J. Physiol.* **27**:60-86, 1910.
42. Dott, N. M., and Bailey, P.: Hypophysial Adenomata, *Brit. J. Surg.* **13**:314-366, 1925.
43. Eaves, E. C.: Changes in the Pituitary After Repeated Injections of Insulin (Preliminary Communication), *J. Physiol.* **62**:vii-viii, 1926-1927.
44. Edinger, L.: Die Ausführwege der Hypophyse, *Arch. f. mikr. Anat.* **78**:496-505, 1911.
45. Engelbach, W.: The Growth Hormone, *Endocrinology* **16**:1-19, 1932.
46. Engle, E. T.: The Effect of Daily Transplants of the Anterior Lobe from Gonadectomized Rats on Immature Test Animals, *Am. J. Physiol.* **88**:101-106, 1929.
47. Erdheim, J.: Zur normalen und pathologischen Histologie der Glandula thyreoidea, parathyreoidea und Hypophysis, *Beitr. z. path. Anat. u. z. allg. Path.* **33**:158-236, 1903.
48. ———Ueber Hypophysenganggeschwülste und Hirncholesteatome, *Sitzungsb. d. k. Akad. d. Wissensch.* **113**:537-726, 1904.

49. Evans, H. M.; Cornish, R. E., and Simpson, M. E.: Potent, Sterile and Low-Protein Extracts of the Growth Hormone from the Anterior Hypophysis, *Proc. Soc. Exper. Biol. & Med.* **27**:101-102, 1929.
50. —and Long, J. A.: The Effect of the Anterior Lobe Administered Intraperitoneally upon Growth, Maturity and Oestrous Cycles of the Rat, *Anat. Rec.* **21**:62-63, 1921.
51. —Myer, K., and Simpson, M. E.: Relation of Prolan to Anterior Hypophyseal Hormones, *Proc. Soc. Exper. Biol. & Med.* **28**:845-847, 1931.
52. —and Simpson, M. E.: Antagonism of Growth and Sex Hormones of the Anterior Hypophysis, *J. A. M. A.* **91**:1337-1338 (Nov. 3) 1928.
53. —Hormones of the Anterior Hypophysis, *Am. J. Physiol.* **98**:511-546, 1931.
54. Fevold, H. L.; Hisaw, F. L., and Leonard, S. L.: The Gonad-Stimulating and the Luteinizing Hormones of the Anterior Lobe of the Hypophysis, *Am. J. Physiol.* **97**:291-301, 1931.
55. Fritsche and Klebs, E.: Ein Beitrag zur Pathologie des Riesenwuchses, Leipzig, F. C. W. Vogel, 1884, 89 pp.
56. Fröhlich, A.: Ein Fall von Tumor der Hypophysis cerebri ohne Akromegalie, *Wien. klin. Rundschau* **15**:883-906, 1901.
57. Geiling, E. M. K.; Campbell, D., and Ishikawa, Y.: The Effect of Insulin on Hypophysectomized Dogs, *J. Pharmacol. & Exper. Therap.* **31**:247-268, 1927.
58. —and DeLawder, A. M.: Metabolic Changes Following the Intravenous Injection of Posterior Pituitary Extracts and Their Correlation with the Well-Known Pharmacodynamic Actions of the Drugs, *Bull. Johns Hopkins Hosp.* **51**:1-26, 1932.
59. —and Eddy, C. A.: The Hyperglycemic Effect of Vasopressin, Oxytocin and Pituitrin, *Proc. Soc. Exper. Biol. & Med.* **26**:146-147, 1928-1929.
60. Goetsch, E.; Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri, *Bull. Johns Hopkins Hosp.* **22**:165-190, 1911.
61. Grollman, A., and Geiling, E. M. K.: The Cardiovascular and Metabolic Reactions of Man to the Intramuscular Injection of Posterior Pituitary Liquid (Pituitrin), Pitressin and Pitocin, *J. Pharmacol. & Exper. Therap.* **46**:447-460, 1932.
62. Guizzetti, P.: Sulle cellule basofile dell' hypophysis cerebri dell' uomo, *Pathologica* **25**:1-10, 1933.
63. Halsted, W. S.: Auto- and Isotransplantation in Dogs, of the Parathyroid Glandules, *J. Exper. Med.* **11**:175-199, 1909.
64. Hartman, C. G.; Firor, W. M., and Geiling, E. M. K.: The Anterior Lobe and Menstruation, *Am. J. Physiol.* **95**:662-669, 1930.
65. Henderson, W. R.: Sexual Dysfunction in Adenomas of the Pituitary Body, *Endocrinology* **15**:111-127, 1931.
66. Hermstein, A.: Striae cutis distensae und Hypophysentumor, *Arch. f. Dermat. u. Syph.* **146**:360-362, 1924.
67. Herring, P. T.: The Histological Appearances of the Mammalian Pituitary Body, *Quart. J. Exper. Physiol.* **1**:121-159, 1908; The Effects of Thyroidectomy upon the Mammalian Pituitary, *ibid.*, pp. 281-285.
68. Höppli, R.: Ueber das Strukturbild der menschlichen Hypophyse bei Nierenerkrankungen, *Frankfurt. Ztschr. f. Path.* **26**:22-49, 1922.
69. Hofbauer, J.: Die Ätiologie der Eklampsie, *Zentralbl. f. Gynäk.* **42**:745-757, 1918.

70. Hoffmann, F., and Anselmino, K. J.: Ueber die Entstehung der Nephropathie und Ekklampsie der Schwangeren, *Klin. Wchnschr.* **31**:1442-1445, 1931.

71. Houssay, B. A., and Biasotti, A.: The Hypophysis, Carbohydrate Metabolism and Diabetes, *Endocrinology* **15**:510-523, 1931.

72. —and Magenta, M. A.: Sensibilidad en los perros hipofisoprivos a la insulina, *Rev. Asoc. méd. argent. (Soc. de biol.)* **37**:389-406, 1924.

73. Janssen, S., and Loeser, A.: Die Wirkung des Hypophysenvorderlappens auf die Schilddrüse, *Arch. f. exper. Path. u. Pharmakol.* **163**:517-529, 1931; *ibid.* **166**:693-702, 1932.

74. Junkmann, K., and Schoeller, W.: Ueber das Thyreotrope Hormon des Hypophysenvorderlappens, *Klin. Wchnschr.* **11**:1176-1177, 1932.

75. Kraus, E. J.: Pankreas und Hypophyse (Eine tierexperimentelle Studie), *Beitr. z. path. Anat. u. z. allg. Path.* **68**:258-277, 1921.

76. —Zur Pathogenese der Dystrophia adiposogenitalis, *Med. Klin.* **20**:1290 and 1328, 1924.

77. —Zur Pathologie des Morbus Addisoni (Befunde in Hypophyse und Nebennieren), *Beitr. z. path. Anat. u. z. allg. Path.* **78**:283-296, 1927.

78. —Ueber die Bedeutung der basophilen Zellen des menschlichen Hirnanhangs auf Grund morphologischer Studien, *Med. Klin.* **24**:623 and 662, 1928.

79. —Welche Zellen der menschlichen Hypophyse bilden ausserhalb der Schwangerschaft das Vorderlappengeschlechtshormon (VLGH)? *Klin. Wchnschr.* **11**:1020-1021, 1932.

80. —and Traube, O.: Ueber die Bedeutung der basophilen Zellen der menschlichen Hypophyse, *Virchows Arch. f. path. Anat.* **268**:315-345, 1928.

81. Lewis, D.: Hyperplasia of the Chromophile Cells of the Hypophysis as the Cause of Acromegaly, with Report of a Case, *Bull. Johns Hopkins Hosp.* **16**:157-164, 1905.

82. —and Lee, F. C.: On the Glandular Elements in the Posterior Lobe of the Human Hypophysis, *Bull. Johns Hopkins Hosp.* **41**:241-277, 1927.

83. Leyton, O.; Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus with Pluriglandular Disturbance, *J. Path. & Bact.* **34**:635-660, 1931.

84. Livon, C.: Pénétration par la voie nerveuse de la sécrétion interne de l'hypophyse, *Compt. rend. Soc. de biol.* **65**:744-745, 1908.

85. Löwenstein, C.: Die Entwicklung der Hypophysisadenome, *Virchows Arch. f. path. Anat.* **188**:44-65, 1907.

86. Lucien, M.: Les cellules cyanophiles du lobe postérieur de l'hypophyse humaine, *Compt. rend. Soc. de biol.* **67**:743-744, 1909.

87. Manley, O. T., and Marine, D.: The Transplantation of Ductless Glands, with Reference to Permanence and Function, *J. A. M. A.* **67**:260-262 (July 22) 1916.

88. Moehlig, R. C.: Basophilic Adenoma of the Pituitary (Pituitary Basophilism), *J. A. M. A.* **99**:1498-1500 (Oct. 29) 1932.

89. Molineus: Ueber die multiplen braunen Tumoren bei Osteomalacie, *Arch. f. klin. Chir.* **101**:333-368, 1913.

90. Mooser, H.: Ein Fall von endogener Fettsucht mit hochgradiger Osteoporose. Ein Beitrag zur Pathologie der inneren Sekretion, *Virchows Arch. f. path. Anat.* **229**:247-271, 1921.

91. Nitzescu, I. I., and Benetato, G.: Action des principes hypertenseur (pitressin) et ocytocique (pitocin) posthypophysaires sur la glycémie et le phosphore anorganique du sang, *Compt. rend. Soc. de biol.* **103**:1359-1362, 1930.

92. Oppenheimer, B. S., and Fishberg, A. M.: The Association of Hypertension with Suprarenal Tumors, *Arch. Int. Med.* **34**:631-644 (Nov. 24) 1924.

93. Parkes Weber, F.: Cutaneous Striae, Purpura, High Blood-Pressure, Amenorrhœa and Obesity, of the Type Sometimes Connected with Cortical Tumours of the Adrenal Glands, Occurring in the Absence of Any Such Tumour, *Brit. J. Dermat.* **38**:1-19, 1926.

94. Penfield, W.: Diencephalic Autonomic Epilepsy, *Arch. Neurol. & Psychiat.* **22**:358-374 (Aug.) 1929.

95. Philipp, E.: Die Bildungsstätte des "Hypophysenvorderlappenhormons" in der Gravidität, *Zentralbl. f. Gynäk.* **54**:1858-1866, 1930.

96. Plaut, A.: Die Stellung der Pars Intermedia in Hypophysenapparat des Menschen, *Klin. Wchnschr.* **1**:1557-1558, 1922.

97. Popa, G., and Fielding, U.: A Portal Circulation from the Pituitary to the Hypothalamic Region, *J. Anat.* **65**:88-91, 1930.

98. Putnam, T. J.; Teel, H. M., and Benedict, E. B.: The Preparation of a Sterile, Active Extract from the Anterior Lobe of the Hypophysis, *Am. J. Physiol.* **84**:157-164, 1928.

99. —Teel, H. M., and Benedict, E. B.: Studies in Acromegaly: VIII. Experimental Canine Acromegaly Produced by Injection of Anterior Lobe Pituitary Extract, *Arch. Surg.* **18**:1708-1736 (April) 1929.

100. Raab, W.: Klinische und röntgenologische Beiträge zur hypophysären und zerebralen Fettsucht und Genitalatrophie (Case 2), *Wien. Arch. f. inn. Med.* **7**:443-530, 1924.

101. Rasmussen, A. T.: Seasonal Changes in the Interstitial Cells of the Testis in the Woodchuck (*Marmota monax*), *Am. J. Anat.* **22**:475-514, 1917.

102. —The Hypophysis Cerebri of the Woodchuck (*Marmota monax*) with Special Reference to Hibernation and Inanition, *Endocrinology* **5**:33-66, 1921; The So-Called Hibernating Gland, *J. Morphol.* **38**:147-205, 1923.

103. —Interstitial Cells of the Testis. Cowdry: Special Cytology, New York, Paul B. Hoeber, Inc., 1928, vol. 2, pp. 1211-1256.

104. —The Percentage of the Different Types of Cells in the Male Adult Human Hypophysis, *Am. J. Path.* **5**:263-274, 1929.

105. Reichert, F. L.: The Results of Replacement Therapy in an Hypophysectomized Puppy: Four Months of Treatment with Daily Pituitary Heterotransplants, *Endocrinology* **12**:451-466, 1928.

106. —Effects of Anterior Pituitary Extract upon an Hypophysectomized Puppy, *Proc. Soc. Exper. Biol. & Med.* **27**:204-205, 1929.

107. Reichmann, V.: Ueber ein ungewöhnliches Krankheitsbild bei Hypophysenadenom, *Deutsches Arch. f. klin. Med.* **130**:133-150, 1919.

108. Riddle, O.: Studies on Pituitary Functions, *Endocrinology* **15**:307-314, 1930.

109. —and Braucher, P. F.: Control of the Special Secretion of the Crop-Gland in Pigeons by an Anterior Pituitary Hormone, *Am. J. Physiol.* **97**:617-625, 1931.

110. —Bates, R. W., and Dykshorn, S. W.: A New Hormone of the Anterior Pituitary, *Proc. Soc. Exper. Biol. & Med.* **29**:1211-1212, 1932.

111. Schmorl: Ein Fall von deformierender Osteitis, *München. med. Wchnschr.* **59**:2891-2892, 1912.

112. Severinghaus, A. E.: A Cytological Technique for the Study of the Anterior Lobe of the Hypophysis, *Anat. Rec.* **53**:1-5, 1932.

113. —The Effect of Castration in the Guinea Pig upon the Sex-Maturing Potency of the Anterior Pituitary, *Am. J. Physiol.* **101**:309-315, 1932.
114. Smith, P. E.: The Disabilities Caused by Hypophysectomy and Their Repair, *J. A. M. A.* **88**:158-161 (Jan. 15) 1927.
115. —Hypophysectomy and a Replacement Therapy in the Rat, *Am. J. Anat.* **45**:205-273, 1930.
116. —and Engle, E. T.: Experimental Evidence Regarding the Rôle of the Anterior Pituitary in the Development and Regulation of the Genital System, *Am. J. Anat.* **40**:159-217, 1927.
117. —and MacDowell, E. C.: An Hereditary Anterior-Pituitary Deficiency in the Mouse, *Anat. Rec.* **46**:249-257, 1930.
118. —The Differential Effect of Hereditary Mouse Dwarfism on the Anterior-Pituitary Hormone, *Anat. Rec.* **50**:85-93, 1931.
119. —and Smith, I. P.: The Response of the Hypophysectomized Tadpole to the Intraperitoneal Injection of the Various Lobes and Colloid of the Bovine Hypophysis, *Anat. Rec.* **25**:150, 1923.
120. —The Topographical Separation in the Bovine Anterior Hypophysis of the Principle Reacting with the Endocrine System from that Controlling General Body Growth, with Suggestions as to the Cell Types Elaborating These Excretions, *Anat. Rec.* **25**:150-151, 1923.
121. Stricker, P., and Grüter, F.: Influence des extraits du lobe antérieur sur l'appareil génital de la lapine et sur la montée laiteuse, *Presse méd.* **37**:1268-1271, 1929.
122. Swingle, W. W., and Pfiffner, J. J.: The Adrenal Cortical Hormone, *Medicine* **11**:371-433, 1932.
123. —Pfiffner, J. J.; Vars, H. M.; Bott, P. A., and Parkins, W. M.: The Function of the Adrenal Cortical Hormone and the Cause of Death from Adrenal Insufficiency, *Science* **77**:58-64, 1933.
124. —Smith, H. M.: A Method for Purification of Extracts Containing the Growth-Promoting Principle of the Anterior Hypophysis, *Science* **69**:405-406, 1929.
125. —The Effect of the Growth Principle of the Hypophysis on the Female Genital Tract, with the Report of the Hypertrophic Changes in a Case of Acromegaly, *Endocrinology* **13**:521-528, 1929.
126. —Basophilic Adenoma of the Hypophysis with Associated Pluriglandular Syndrome, *Arch. Neurol. & Psychiat.* **26**:593-599 (Sept.) 1931.
127. —and Cushing, H.: Studies in the Physiological Properties of the Growth-Promoting Extracts of the Anterior Hypophysis, *Endocrinology* **14**:157-163, 1930.
128. —and Watkins, O.: The Effect of Extracts Containing the Growth Principle of the Anterior Hypophysis upon the Blood Chemistry of Dogs, *Am. J. Physiol.* **89**:662-685, 1929.
129. Thaon, P.: Note sur la sécrétion de l'hypophyse et ses vaisseaux évacuateurs, *Compt. rend. Soc. de biol.* **62**:714-716, 1907.
130. Thom, W.: Untersuchungen über die normale und pathologische Hypophysis cerebri des Menschen, *Arch. f. mikr. Anat.* **57**:632-652, 1901.
131. Thomson, D. L., and Pugsley, L. I.: On the Mechanism of Parathyroid Hormone Action, *Am. J. Physiol.* **102**:350-354, 1932.
132. Tölken, R.: Zur Pathologie der Hypophysis, *Mitt. a. d. Grenzgeb. d. Med. u. Chir.* **24**:633-644, 1912.

133. Turney, H. G.: Discussion on Disease of the Pituitary Body, Proc. Roy. Soc. Med. (Sec. Neurol. & Ophth.) **6**:1xix-lxxviii, 1913.

134. Weed, L. H.; Cushing, H., and Jacobson, C.: Further Studies on the Rôle of the Hypophysis in the Metabolism of Carbohydrates: The Autonomic Control of the Pituitary Gland, Bull. Johns Hopkins Hosp. **24**:40-52, 1913.

135. Wieth-Pedersen, G.: Et tilfaelde af binyretumor og et af hypofysetumor med binyrehyperplasi, begge med Striae distinsae cutis, Hospitalstid. **74**:1231-1244, 1931.

136. Zondek, B.: Ueber die Hormone des Hypophysenvorderlappens, Klin. Wchnschr. **9**:245, 393, 679 and 1207, 1930.

137. —Prolan in der Hypophyse: II. Produktion des Prolans in den basophilen Zellen, Klin. Wchnschr. **12**:22-24, 1933.

138. —and Krohn, H.: Hormon des Zwischenlappens der Hypophyse (Intermedin), Klin. Wchnschr. **11**:405, 849 and 1293, 1932.

139. —"Die Krankheiten der Endokrinen Drüsen," Berlin, Julius Springer, 1923.

